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# THE ABSORPTION, EXCRETION AND TOXICITY OF STREPTOMYCIN IN MAN*

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IN JANUARY, 1944, Schatz, Bugie and Waksman[1] described the isolation of a new antibacterial substance from the culture filtrate of *Actinomyces griseus*. They named this substance "streptomycin" and reported that it had a marked antibacterial action in vitro against many gram-negative and gram-positive bacteria. According to its discoverers, streptomycin resembled streptothricin, another antibacterial agent isolated in 1942,[2] but had a wider bacteriostatic spectrum and was quantitatively more active against certain organisms and less toxic for animals.

Several studies[3–9] have now been reported in which it has been shown that streptomycin is sufficiently effective in vivo in the treatment of experimental infections in animals with various gram-negative bacteria and *Mycobacterium tuberculosis* to warrant an extended clinical investigation of its value in the treatment of human infections. To date, only one report[10] has been published describing the use of streptomycin in the treatment of established infections in man. Other clinical studies are now being carried out by various investigators, and as the production of streptomycin increases, further information regarding its effectiveness as a chemotherapeutic agent should soon be forthcoming.

The purpose of this paper is to report certain preliminary studies carried out on the absorption and excretion of streptomycin in man. In addition, brief mention is made of 3 cases in which the drug was used therapeutically. Finally, the toxic reactions observed are described.

## MATERIALS AND METHODS

All subjects used for the pharmacologic studies were adult ward patients who presented no evidence of any impairment of renal function.

Streptomycin was dissolved in distilled water for intravenous, intramuscular and subcutaneous administration in concentrations varying from 50,000 to 150,000 units per cubic centimeter. The solutions used for intrathecal administration varied in concentration from 2500 to 5000 units per cubic centimeter. Although streptomycin has been shown to be relatively heat stable and to be capable of withstanding room temperatures for extended periods of time, the various solutions of the drug were stored at 5°C. until time of use.

The samples of blood that were assayed for streptomycin were taken under sterile precautions and allowed to clot in sterile tubes. The serum was then separated by centrifugalization.

All studies on the urinary excretion of streptomycin were carried out in male patients, the patients voiding into sterile containers.

All samples of body fluids were stored at 5°C. until they were tested. All but a few specimens were tested on the same day that they were obtained.

The method of assay used was the cup-plate method described by Stebbins and Robinson,[11] in which *Staphylococcus aureus* (Strain SM) is employed as the test organism. The only modification of the method was the use of horse serum instead of the patient's serum to dilute the standard solutions used in assaying serum specimens. This modification was made for the sake of convenience after it had been determined that the substitution of horse serum did not alter the diameter of the zone of inhibition obtained with the standard amounts of the drug used in the method.

This method has proved to be extremely satisfactory for the determination of concentrations of streptomycin in body fluids varying from 1 to 12 units per cubic centimeter, and only slightly less satisfactory for concentrations up to 20 units per cubic centimeter. Within these ranges relatively consistent and reproducible results have been obtained. When higher or lower concentrations of streptomycin have been encountered, the results of replicate tests have shown less consistency. The determinations done on urine specimens, in which

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The streptomycin used in this study was supplied through the courtesy of Merck and Company, Rahway, New Jersey, from supplies allocated to the Committee on Chemotherapeutics and Other Agents, National Research Council, for investigations on the toxicology, absorption and excretion of streptomycin.

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high concentrations of streptomycin were frequently encountered, probably have a fairly high margin of error and should be considered as representing only approximate values. The only other significant problem met within the cup-plate method was that of occasional technical difficulty in securing even, regular zones of inhibition about the cups.

In the pharmacologic studies, all determinations were made in duplicate and many of them in triplicate. When irregularity of the zones of inhibition rendered a test unsatisfactory, it was repeated. The final value assigned to any determination was the average of the replicates computed to the nearest whole unit.

The streptomycin unit has been defined by Robinson and his associates[4] as that quantity of the antibiotic agent that inhibits the growth of a given strain of *Escherichia coli* in 1 cc. of nutrient broth or agar. They have reported the production of preparations of streptomycin that contain 500 units per milligram.

For the purposes of orientation, it should be pointed out that a unit of streptomycin represents a much smaller amount of antibacterial activity than does a unit of penicillin. Thus, when the action of the two substances is studied against *Staph. aureus* (Strain SM), an organism against which both drugs are active, it is found that the growth of this organism is just completely inhibited by 0.08 units of penicillin, whereas the smallest amount of streptomycin that causes complete inhibition is 1 unit. It is therefore apparent that a unit of penicillin represents approximately twelve times as much antibacterial activity for this test organism as does a unit of streptomycin.

## Absorption of Streptomycin with Various Routes of Administration

### *Oral Administration*

Six hundred thousand units of streptomycin dissolved in 100 cc. of tap water was administered orally to 1 patient in the fasting state. The serum was tested for its streptomycin content at frequent intervals during the next twelve hours. *No drug was detected in the serum at any time.* A solution containing 20 units of streptomycin per cubic centimeter was then incubated at 37°C. for three hours with an equal volume of gastric juice containing free hydrochloric acid. Assay of the mixture at the end of the period of incubation showed that the exposure to gastric juice for three hours had resulted in no loss of the drug's activity.

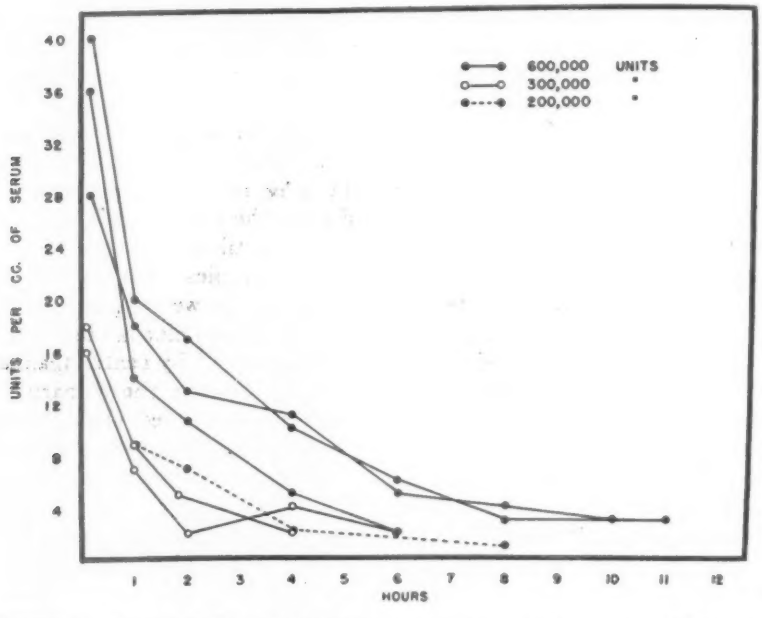


Figure 1. *Concentrations of Streptomycin in Serum following the Intravenous Injection of Varying Doses.*

### *Intravenous Administration*

Figure 1 shows the concentrations of streptomycin in the serum at varying intervals after the intravenous injection of single doses of the drug in different cases. The highest levels were obtained within five minutes after injection. Individual variations were observed, but the levels were in general proportional to the amount injected. During the first hour after injection the concentration in the serum decreased rapidly, but in the succeeding hours the fall was more gradual. With the smallest dose administered, 200,000 units, a concentration

of 1 unit per cubic centimeter was still detectable in the serum at the end of eight hours. After the injection of 600,000 units, the largest dose administered, the serum still contained 3 units per cubic centimeter at the end of eleven hours.

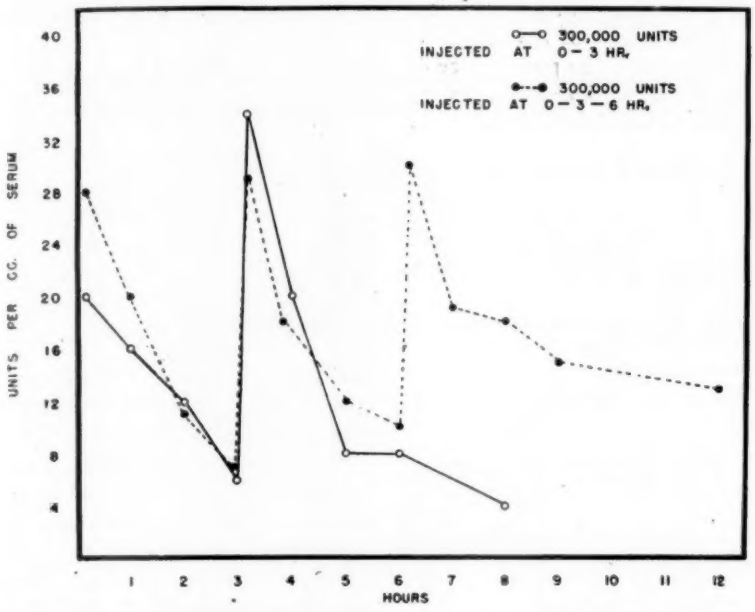


FIGURE 2. *Concentrations of Streptomycin in Serum following Multiple Intravenous Injections at Three-Hour Intervals.*

Figure 2 shows the serum concentrations in 2 patients receiving multiple intravenous injections of 300,000 units each at three-hour intervals. The effect of repeating the injections at short intervals was to produce somewhat higher serum levels than those observed at similar intervals after a single injection. The higher levels so obtained appeared merely to reflect the accumulation of the drug in the body.

*Intramuscular Administration*

Figure 3 shows the concentrations of the drug observed in the serum at varying intervals after the intramuscular administration of single injections into

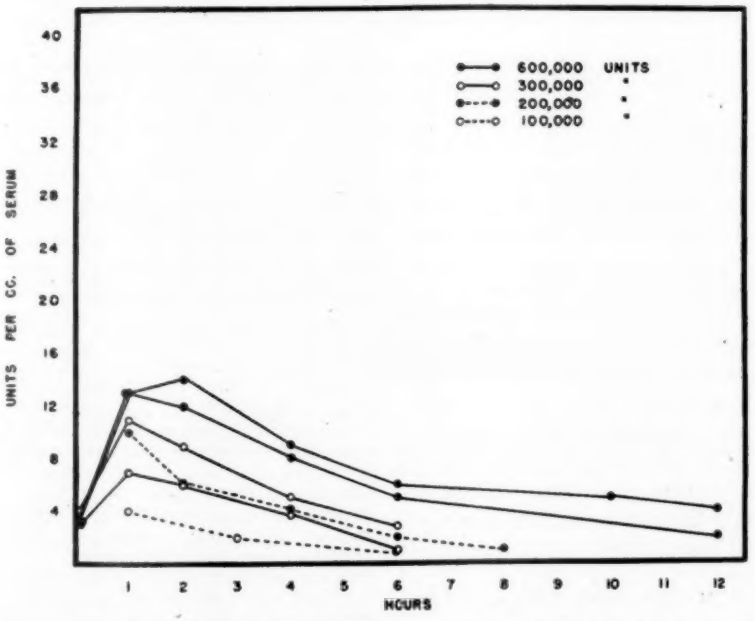


FIGURE 3. *Concentrations of Streptomycin in Serum following Intramuscular Injection of Varying Doses.*

the gluteal muscles. The only essential difference between these results and those observed after intravenous injection was that the concentrations found in the serum five minutes after intramuscular injection were much lower. The height of the levels at the other points on the curve and the persistence of the drug in the serum after a given dose did not vary significantly with the route of administration.

### Excretion of Streptomycin in the Urine

In Table 1 is shown the total twenty-four-hour excretion of streptomycin in the urine as observed in 4 subjects. The amount of drug excreted in twenty-four hours varied from 46 to 66 per cent and averaged 57 per cent of the dose injected.

Table 1. *Twenty-Four-Hour Excretion of Single Doses of Streptomycin in the Urine.*

| Dose | Route of Injection | Urinary Excretion |
|---|---|---|
| *units* | | % |
| 600 000 | Intravenous | 50 |
| 600 000 | Intravenous | 66 |
| 600 000 | Intravenous | 46 |
| 600,000 | Intramuscular | 64 |
| Average | | 57 |

The rate of excretion at various intervals after injection is shown in Table 2. Although excretion was greatest during the first four hours after administration, one fifth to one third of the dose injected was not excreted until between the fourth and the twelfth hour. The excretion during the interval between the twelfth and the twenty-fourth hour was studied in only 1 case, in which only very small amounts of streptomycin appeared in the urine after the twelfth hour. Traces of the drug, however, could still be detected between the twenty-fourth and the thirtieth hour after injection.

From these figures it can be concluded that the urinary excretion of streptomycin is significantly slower than that of penicillin, since after intramuscular or intravenous injection an average of 60 per cent of the dose of penicillin injected can be recovered in the urine within one hour. Likewise, the excretion of a single dose of penicillin is nearly complete by the end of four hours.

### Diffusion of Streptomycin into Spinal Fluid

Studies of the diffusion of streptomycin from the blood into the spinal fluid were carried out in a patient suspected of having tuberculous meningitis. The cerebrospinal fluid was tested for its streptomycin content on four separate days at intervals varying from two to eight and a half hours after the parenteral administration of doses of 200,000 and 300,000 units of streptomycin. Simultaneous serum levels were determined, and by coincidence were 5 units per cubic centimeter on each occasion. On two days the spinal fluid showed merely a trace of streptomycin, whereas on the other two days readings of 1 unit per cubic centimeter were obtained.

Table 3. *Streptomycin Levels in the Cerebrospinal Fluid after Intrathecal Administration.**

| Dose | 24-Hr. Spinal-Fluid Level | 24-Hr. Serum Level |
|---|---|---|
| *units* | *units/cc.* | *units/cc.* |
| 5,000 | 6 | 1 |
| 10,000 | 7 | 2 |
| 10,000 | 5 | 4 |
| 15,000 | 6 | 4 |
| 15,000 | 7 | 2 |
| 20,000 | 14 | 2 |

*Intramuscular therapy at a dosage of 300,000 units every 12 hours was being administered simultaneously.

Streptomycin was then administered intrathecally to the same patient. Intramuscular therapy at a dosage of 300,000 units every twelve hours was administered simultaneously. The levels obtained in the cerebrospinal fluid twenty-four hours after the administration of various doses and the simultaneous serum levels are shown in Table 3. These results indicate that following the intrathecal administration of streptomycin, the absorption of the drug from the subarachnoid space is not complete by the end of twenty-four hours.

Table 2. *Excretion of a Single Dose of Streptomycin in the Urine at Varying Intervals after Administration.*

| Dose | Route of Injection | Urinary Excretion in Hours 0–1 | 2–3 | 4–11 | 12–23 | 24–30 | Total Excretion |
|---|---|---|---|---|---|---|---|
| *units* | | % | % | % | % | % | % |
| 200,000 | Intramuscular | 33 | 30 | Not done | Not done | Not done | 63 (4 hr.) |
| 300,000 | Intramuscular | 33 | 15 | 20 | 3 | 1 | 72 (30 hr.) |
| 600,000 | Intramuscular | 39 | 16 | 32 | Not done | Not done | 87 (12 hr.) |

### Case Reports

To date we have had an opportunity to administer streptomycin in therapeutic doses to only 3 patients. These cases are reported briefly, chiefly to illustrate the apparent lack of significant toxicity following the prolonged administration of streptomycin.

Case 1 (Fig. 4). V. H., a 17-year-old Negress, entered the hospital for fusion of the right knee because of tuberculous synovitis. For the first 2 weeks after operation, convalescence was satisfactory. On the 15th postoperative day, there was a sudden chill and the temperature rose to 104.4°F. There were no localizing signs or symptoms. A blood culture was obtained the following day and 48 hours later was reported to be positive for *Eberthella typhosus*. Subsequent studies showed that this organism was completely inhibited in vitro by 12 units of streptomycin per cubic centimeter of media.

When the positive blood culture was reported, streptomycin therapy was started at a dosage of 30,000 units intramuscularly every 4 hours. After 72 hours the supply of streptomycin was temporarily exhausted. Twenty-four hours later, the 9th day of the illness, a fresh supply of drug was received and treatment was resumed at a dosage of 125,000 units intramuscularly every 3 hours. After this dosage had been administered for 48 hours, the blood culture became negative. A blood culture taken 2 days later, however, proved to be positive. When this report was received, the dosage was

increased to 200,000 units every 3 hours. This dosage was continued for the next 7 days, at which time treatment was discontinued.

From the chart it can be seen that the blood culture became permanently negative before the dosage was increased from 125,000 to 200,000 units every 3 hours. The urine culture was never positive, and except for one positive culture on the 6th day of the illness, *E. typhosus* was never recovered from the stool.

The temperature, which had been sustained between 103 and 105°F. during the first 9 days of the illness, declined by lysis during the 1st week of treatment with the larger doses. During the 2nd week it gradually rose again to 103°F. but fell to normal the day after streptomycin was discontinued. Thereafter it remained below 100°F.

Symptomatically the response to treatment was not striking. The patient remained lethargic and suffered from severe anorexia until she had received 1,000,000 units of streptomycin daily for 7 days. At that time, the 15th day of the illness, she began to have a desire for food and appeared somewhat more alert. Thereafter there was slow but progressive improvement. Rather marked lethargy persisted, however, until 6 days after streptomycin was discontinued. From then on the patient appeared to have recovered fully from the acute illness, and her subsequent convalescence was uneventful.

*Comment.* The evaluation of the effect of the streptomycin therapy in this case is difficult. The patient's clinical and bacteriologic course is suggestive, but not conclusive, of a definite therapeutic response to streptomycin.

This patient received a total of 18,150,000 units of streptomycin over a period of 20 days. During this time repeated blood counts and urinalyses showed no evidence that streptomycin had any harmful effect on the hematopoietic system or on the kidneys. The patient did complain continually of pain following the intramuscular injections, and during the last 2 weeks of treatment the buttocks were indurated and extremely tender. In view of the prompt return of the temperature to normal after streptomycin was discontinued, it seems reasonable to ascribe the rising fever during the last week of treatment to the drug.

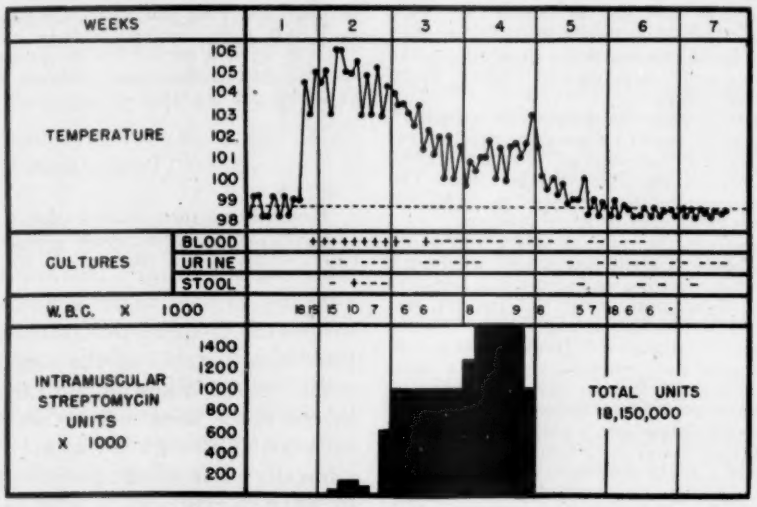


FIGURE 4. *Chart of a Patient with Typhoid Fever (Case 1) Treated with Streptomycin.*

*The patient's clinical and bacteriologic course was suggestive, but not conclusive, of a definite therapeutic response to streptomycin.*

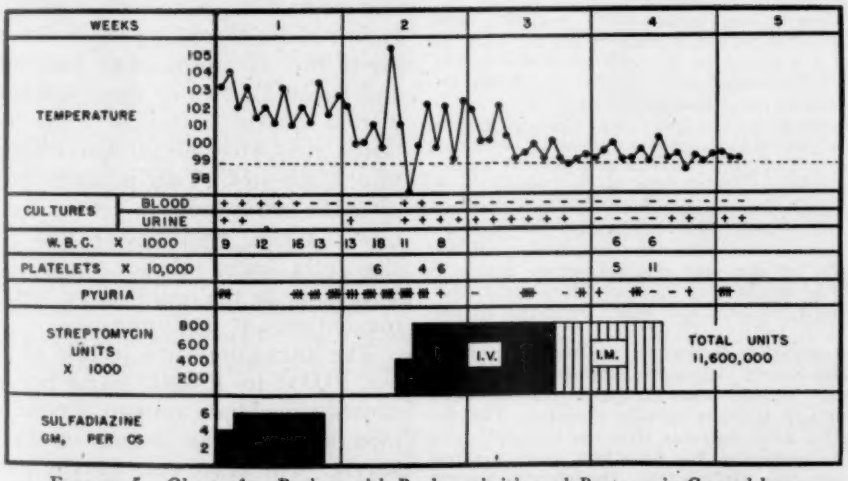


FIGURE 5. *Chart of a Patient with Pyelonephritis and Bacteremia Caused by a Group B Salmonella (Case 2) Treated with Streptomycin.*

*The illness was complicated by thrombocytopenia with severe epistaxes. The effect of streptomycin therapy was difficult to evaluate.*

CASE 2 (Fig. 5). J. G., a 46-year-old American Indian, had had diabetes mellitus for 7 years. Fifteen days before ad-

mission to the hospital he had had a shaking chill and had developed dull aching pain in both loins. The next day the urine became cloudy and there was burning pain on urination. The fever, pain and dysuria persisted for the next 2 weeks, during which time the patient remained in bed at home without receiving specific therapy. At the end of that time he was referred to the hospital by his physician.

On physical examination the patient appeared acutely ill. The only positive physical findings of significance were marked bilateral costovertebral-angle tenderness and marked prostatic tenderness on rectal examination. In addition, the prostate gland was moderately enlarged and boggy. There were no signs of a prostatic abscess.

Blood and urine cultures on entry to the hospital were both positive for a gram-negative bacillus that gave the fermentation reactions of a Group B Salmonella. (Further studies to complete its identification are being carried out.) The organism was found to be completely inhibited in vitro by 4 units of streptomycin per cubic centimeter of medium.

Immediately on admission the patient was given sulfadiazine, 1 gm. every 4 hours. On the 6th day of treatment, the blood culture became negative and remained negative for the next 4 days. Symptomatically the patient was markedly improved, the costovertebral-angle pain and the dysuria having entirely disappeared. Improvement continued until the 8th hospital day, when there began a series of severe spontaneous epistaxes. Within 48 hours the hematocrit fell from 40 to 30 per cent. The platelets were markedly reduced, numbering only 64,000 per cubic millimeter. During the next 36 hours the patient received 1500 cc. of whole blood by transfusion, with only a slight decrease in the amount of bleeding.

Treatment with streptomycin was started on the 11th hospital day at a dosage of 200,000 units intravenously every 6 hours. After 9 days of treatment, intravenous therapy was discontinued and the same dosage was given by intramuscular injection. Treatment was continued for another 6 days.

A blood culture taken just before streptomycin was begun and another taken 24 hours later were positive for the same organism that had been recovered from the blood and urine on entry. From that time on, however, all blood cultures were negative. The urine culture remained positive until the last 4 days of treatment and again became positive the day after streptomycin was discontinued.

The temperature remained elevated until the 8th day of treatment. Thereafter it was below 100°F. rectally until the last day of treatment, when it rose to 100.4°F. for 12 hours. The patient had recovered from his acute discomfort before streptomycin was started, and reliance in judging his progress had to be placed on objective findings.

The epistaxes continued for the first 5 days of streptomycin therapy. On the 3rd day of treatment, numerous petechiae appeared in the skin and conjunctivas and several flame-shaped hemorrhages were seen in the ocular fundi. New petechiae kept appearing for the next 2 days. Thereafter, no new hemorrhagic phenomena were observed. Although no significant rise in the platelet count was observed until the last day of therapy, 50 per cent clot retraction within 2 hours was observed from the 12th day on. Previous to this time the 2-hour clot retraction had never exceeded 20 per cent.

*Comment.* The evaluation of the effectiveness of streptomycin therapy in this case is even more difficult than that in Case 1. It is entirely possible that the patient would have improved spontaneously without specific therapy. The reappearance of positive urine cultures after the completion of treatment is clear evidence that the drug had not eliminated the infecting organism from the tissues, although it may have played a role in clearing the organism from the blood stream.

This patient received a total of 11,600,000 units of streptomycin over a period of 15 days. As in the first case, no toxic effects on the kidneys or hematopoietic system were observed. A low-grade fever appeared on the last day of treatment and disappeared when streptomycin was withdrawn.

The intravenous injections were at first well tolerated but later caused flushing of the face, intense headache and nausea. The only ill effects from the intramuscular injections were pain and tenderness at the sites of injection.

CASE 3.* The patient was a 5-year-old girl who had meningitis and bacteremia caused by an organism that had all the cultural characteristics of *Haemophilus influenzae* but that could not be typed with either Type A or Type B antiserum. The organism was completely inhibited in vitro by 0.75 units of streptomycin per cubic centimeter of medium.

After 8 weeks of treatment with sulfadiazine and sulfamerazine, the patient was still acutely ill and cultures of the blood and spinal fluid were both positive. Streptomycin therapy was then instituted, the patient receiving a total of 2,725,000 units intramuscularly and 255,000 units intrathecally over a period of 3½ weeks. There was a prompt clinical and bacteriologic response to the administration of the drug and the patient completely recovered.

*This case is to be reported in detail by Dr. Louis Weinstein in a paper discussing infections caused by atypical strains of *Haemophilus influenzae*.

## TOXIC REACTIONS

Repeated examination of the blood in the patients receiving single doses of streptomycin and in those receiving the drug in therapeutic doses failed to reveal any damage to the hematopoietic system. Daily urinalyses, frequent determinations of the blood nonprotein nitrogen and the measurement of the daily urine volume likewise indicated that streptomycin in the doses used had no deleterious effect on the kidneys. Although it was not tested for specifically, clinically none of the patients showed any evidence of liver damage.

The administration of single doses of the drug caused no febrile reactions. In Cases 1 and 2, attention has already been called to the fact that the patients had fever, which promptly disappeared when treatment was stopped. No skin eruptions were observed in any patients receiving streptomycin.

When intravenous injections of solutions of streptomycin containing 50,000 to 100,000 units per cubic centimeter were given, the patients almost uniformly complained of a peculiar taste in the mouth and a throbbing headache and showed flushing of the face. A marked flush was usually visible and lasted for two or three minutes after the completion of the injection. The headache usually lasted somewhat longer but disappeared in ten to fifteen minutes. Two patients experienced nausea after the intravenous injection of concentrated solutions. When streptomycin was administered in a slow intravenous infusion, doses up to 500,000 units were given in the course of an hour without producing unpleasant symptoms.

The intramuscular injection of solutions containing 50,000 to 100,000 units per cubic centimeter caused a moderate amount of pain immediately after injection, but the degree of discomfort was not severe. The acute pain usually passed off in fifteen to thirty minutes, but some soreness at the site of the injection persisted for one to several hours after a single injection. When multiple intramuscular injections were given, the buttocks became constantly painful, tender and indurated. These findings persisted for as long as a week after the injections were discontinued. Only rarely did an intramuscular injection produce flushing and headache.

In 1 case, the subcutaneous administration of 2 cc. of a solution containing 150,000 units per cubic

centimeter produced pain, tenderness and moderate swelling of the tissues at the site of the injection. The pain lasted for more than an hour, and some tenderness and swelling persisted for forty-eight hours.

The intrathecal administration of streptomycin solutions containing 5000 units per cubic centimeter in amounts up to 4 cc. produced no signs of meningeal irritation. After repeated intrathecal injections over a period of several weeks, 1 patient complained of pain in the back radiating down the posterior aspect of both thighs on coughing or moving.

## Summary and Conclusions

From this study the following conclusions have been drawn:

Streptomycin is not absorbed after oral administration in amounts sufficient to produce detectable concentrations of the drug in the serum.

The failure of the drug to be absorbed from the gastrointestinal tract is not due to the inactivation of streptomycin by the gastric juice.

The curves of the serum concentrations of the drug after the intramuscular or intravenous injection of a given amount of streptomycin do not differ significantly except during the first few minutes after injection.

Following the intramuscular or intravenous administration of a single dose of streptomycin, 46 to 87 per cent of the dose injected can be recovered in the urine within twenty-four hours.

Streptomycin is excreted more slowly by the kidneys than is penicillin. It appears likely that effective blood levels of streptomycin can be maintained by administering the drug at intervals of six to eight hours.

In patients with meningitis, streptomycin diffuses to a slight extent from the blood into the cerebrospinal fluid.

The intrathecal administration of streptomycin in doses up to 20,000 units does not produce signs of meningeal irritation. With doses of 10,000 to 20,000 units, an appreciable concentration of the drug can be maintained in the cerebrospinal fluid for at least twenty-four hours.

No serious toxic reactions apparently follow the injection of single doses of streptomycin in amounts up to 600,000 units or after the continued administration of the drug for periods of two to three weeks in doses totaling 2,725,000 to 18,150,000 units.

The intravenous and subcutaneous injection of concentrated solutions of the present preparations of streptomycin causes too much discomfort to warrant the use of these methods of administration.

The drug can be administered in an intravenous infusion without the production of unpleasant symptoms.

Intramuscular injections are fairly well tolerated for periods up to one to two weeks. Therapy continued beyond these times may cause severe discomfort.

Three cases of infection due to a gram-negative bacillus and treated with streptomycin are reported; no conclusions concerning the efficacy of streptomycin can be drawn from them.

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# RECONSTRUCTIVE SURGERY OF THE WAR WOUNDED*

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THE term "reconstructive surgery" means the making good of physical defects. To reconstruct, according to *Webster's Dictionary*, is "to rebuild, to remodel or to construct again"; hence, the term has a mechanical implication that pertains to a large field of orthopedic surgery. It is a term that was born from the last war after experience with the rebuilding of defects to skin, muscle, nerves, bones and joints resulting from war injuries. It thus has a vital significance today when we have again been at war and confronted with the problem of treating large numbers of battle casualties. My task today is therefore to survey the field of reconstructive surgery in relation to the treatment of those who have been wounded in this war.

## TREATMENT IN ZONE OF COMBAT

From all reports, there can be no doubt that the wounded are receiving better medical care than ever before. This is reflected in some of the figures that have been received; for example, there has been a mortality rate of less than 3.5 per cent among those who reach the hospitals at the front, a recovery rate of 75 per cent for penetrating wounds of the abdomen, and one of 80 per cent for penetrating wounds of the chest.

There are three principal factors that contributed to these results. The first of these — and the chief one, in my opinion — is that proper surgical treatment has been made available much closer to the front than ever before. Field operating hospitals are set up alongside the divisional dressing stations, and all casualties requiring immediate surgical procedures receive them without delay. The second factor is the better and earlier treatment of shock. Undoubtedly little could be done if huge stores of plasma were not available on the spot, but on the other hand, plasma would not accomplish the task if we had not learned how to make the best use of it. Although plasma is good, whole blood is even better, but because of the necessity of typing and cross matching, it is less adaptable to field use. The procurement and delivery of whole blood at the front so that it may be used within the prescribed time period of ten days after it is drawn presented great difficulties, but thanks to fine teamwork between the Army and the American Red Cross and to the miracle of rapid transportation by the airplane, they have been solved. In addition to plasma and whole blood, human albumin and all types of intravenous solutions are available when needed. The conquest of shock among the wounded makes possible earlier and more effective surgical procedures, which in turn help to overcome infection, the second of the twin bugaboos of the military surgeon.

The chief injury in approximately 60 per cent of the wounded is one or more compound fractures. There is generally extensive comminution of the fragments, and often loss of bone substance. There is also severe damage of the soft tissue, including muscle and skin, and not infrequently injury of important nerves. Metallic fragments from explosive missiles or rifle or machine-gun bullets are driven into the soft tissues, where they constitute foreign bodies, carrying with them bits of soiled clothing and débris, including earth, gravel and rubble.

The immediate problem in the treatment of these wounds is the prevention of infection, and here too progress has been made. It is known that early and careful débridement with excision of all contaminated and devitalized tissue and the removal of gross foreign bodies — but with due regard to the preservation of viable bone fragments and important soft structures — goes far toward preventing serious infection. The wounds are left open, lightly packed with plain or vaseline gauze and covered with gauze dressings, and the limbs are then splinted. The closed plaster cast, always split after it is applied, with or without traction by means of adhesive plaster strips whose ends are fastened to the plaster or by skeletal pins incorporated in the plaster, is still the method of choice for splinting and evacuating.

The role of chemotherapy in the prevention of wound infection at the front is still debatable. All the evidence collected by the Subcommittee on Infected Wounds of the National Research Council has tended to belittle the effectiveness of the sulfonamide drugs when used locally in wounds. When placed in an open wound at the time of débridement in cases in which renewal is not possible because of the plaster-of-Paris covering, their effect, if any, is so transient as not to be worth while. On the other hand, there is no dispute about their effectiveness when administered orally in combating the spread of certain organisms, chiefly streptococci and anaerobic gas-producing bacilli. But they may be dangerous when given without checkup by laboratory tests, and such control is frequently impossible near the front. On the whole, it seems

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Owing to the absence of Dr. Wilson, this paper was read by Dr. John Kopf, of New York City.

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a better policy to concentrate on the rapid evacuation of the wounded to hospitals in the rear and to postpone the intensive use of the sulfonamide drugs until their arrival there.

Now that a more effective and safer chemotherapeutic agent is available for the treatment of infection in the form of penicillin, the question arises whether it can be used in forward operating hospitals. Experiments are being conducted with its local use in wounds, and on their outcome depends the decision whether this method is worth while. As for its general use in the forward hospitals, this appears to be unacceptable, except in selected patients who may be held for reasons of safety, because of the difficulty of keeping up the necessary intramuscular or subcutaneous injections during evacuation. On the other hand, penicillin has proved valuable in the treatment of many patients with severely infected wounds after they reach the general hospitals in the rear.

### Treatment in Rear Hospitals

I have discussed the treatment of the wounded at the front, particularly that of those with compound fractures, because the results of such treatment have a great bearing on the reconstructive surgery that must be done later. The same also applies to the intermediate treatment that is carried on in the general hospitals located in safe areas behind the front, to which the wounded are evacuated following primary treatment. A great contribution to their better care has been made by the improvements in transportation and the wider use of the airplane. These make their evacuation quicker and safer.

The function of these hospitals is to provide medical care of the wounded until they are able to return to active duty or, if it is decided that they cannot be so returned, until they are in sufficiently good condition to make the journey by airplane or ship to the United States. According to a directive of the Surgeon General of the Army, no reconstructive surgical operations are to be performed in foreign theaters of operation and all wounded who require such procedures must be returned to this country. Notwithstanding this limitation on their surgical activities, these hospitals are making important contributions to the treatment of the wounded.

All the patients with injuries involving the bones and joints are the responsibility of the orthopedic surgeons, and they have the task of dealing with infected, malunited and ununited fractures and with the injuries of the joints. So far as invasive infections are concerned, including those from the anaerobic gas-producing organisms or the hemolytic streptococci, these are less frequent and better controlled — by penicillin and the sulfonamide drugs — than was the case in the last war. But the gain in this direction has been counterbalanced by the increase in severe compound and comminuted fractures of the lower extremities resulting from the extensive use of land mines. Unfortunately, many amputations must still be performed because of vascular injury, extreme structural damage or gas gangrene, but the indications for such mutilating operations are now better known and more quickly recognized than before, so that more lives are saved.

When patients with compound fractures or joint injuries are admitted to these hospitals in the rear, the first step is to remove the plaster casts in which they were transported and to apply traction, either by adhesive strips or when indicated by skeletal pins, in conjunction with suspension splints. Therefore, the surgical objective so far as the fracture is concerned is to secure the best possible alignment of the fragments and to maintain it until either bony union is obtained or the healing progresses sufficiently to permit encasement in plaster without danger of loss of position, thus permitting transportation to the United States.

But the splinting of the fracture is only one part of the management of these battle-incurred compound fractures; the other part is the treatment of the wounds. There has been quite a swing away from the closed plaster or Orr no-dressing technic that was so popular in the early days of the war. Doubtless this has been motivated partly by the development of more efficient methods of chemotherapy, but successful experiments with secondary wound closure have also played a part.

Experience has shown that when a wound is left open with bone fragments exposed in its depths, sooner or later secondary infection develops even when it was clean primarily. The best method of insurance against secondary infection is to seal the wound by a barrier of intact skin and soft tissue. Primary closure cannot be practiced at the field hospitals because of the danger that would be incurred in early evacuation. On the other hand, when the wounds of compound fractures have been thoroughly débrided and the fractures properly splinted, the patients reach the rear hospitals before infection has developed. Under these circumstances secondary closure by suture or by skin grafts may be attempted with little risk, especially when the patient is protected by the administration of sulfadiazine or penicillin. Experience shows that the earlier the closure is attempted the better are the results. The optimum time is from three to five days, but many successful closures have been obtained after longer periods. Preliminary reports indicate that successful results have been accomplished in 75 to 80 per cent of the cases, and that even when the result was a failure little or no harm to the patient resulted.

Some surgeons advocate internal fixation of the fragments by the use of steel bone plates at the time of the closure, but it is too early to evaluate this procedure. The transformation of compound,

potentially infected fractures into clean closed fractures is a major advance and carries immensely favorable implications for patients who may require surgical reconstruction.

### Surgical Reconstruction in the United States

From this brief survey of the treatment of war injuries involving the bones and joints in the zone of combat and in the rear, certain conclusions may be drawn regarding the task of surgical reconstruction that must be done in the Army and Navy hospitals in the United States. These are the following. Patients will be returned to this country at an earlier period following injury than in the last war. They will arrive in better physical condition than in the last war. In a large number of cases — perhaps as many as 75 per cent — the wounds will be healed. Chronic bone infection is a less serious problem than in the last war, and when present better methods of treatment will be available to deal with it. Many of the patients will be ready for reconstructive surgery as soon as they reach this country, and the long periods of waiting previously required for clearing of infection are no longer necessary. There will be fewer cases of malaligned and malunited fractures than in the last war, and the percentage of cases requiring reconstructive surgery will be smaller.

With this optimistic prediction, which I hope will be substantiated by events, let me turn to a consideration of some of the more frequently encountered conditions that require surgical reconstruction, and the procedures that may be employed in their treatment.

### Chronic Bone Infection

The presence of discharging sinuses with a history of a war wound and a compound fracture is always presumptive evidence of a focus of bone infection. Whether surgical eradication of the focus is to be advised depends on examination of the wound and study of the x-ray films. The introduction of a probe often demonstrates bare bone at the bottom of the sinus, or if this fails, the introduction of radiopaque material and x-ray examination shows the course of the sinus and whether it connects with bone. Study of the x-ray films demonstrates the presence or absence of sequestrums and reveals whether there are infected cavities in the bone that must be cleared out to obtain healing. When the bone is dense, overexposed films sometimes aid considerably in evaluating the situation.

The question is frequently asked whether the administration of penicillin would not obtain healing in such cases and eliminate the need for surgical treatment. Certain investigators have shown that in cases of chronic bone infection the drug does not penetrate to the focus when given parenterally, and that when sequestrums are present it is not effective when given locally in the sinus. Surgical removal of sequestrums and opening and saucerization of bone cavities are just as necessary as ever, but to obtain the best results penicillin should be administered both before and following operation. Under these conditions, many of the wounds with low-grade chronic infections may be closed primarily, or if this seems unwise they may be packed open and closed secondarily at the end of seven to ten days. Immobilization of the extremity, preferably in plaster of Paris, is of great importance in obtaining this result.

Recent studies have shown the value of a high-protein diet and adequate vitamins in promoting wound healing. One investigator has also called attention to a state of chronic surgical shock in many of these patients, which must be combated by the administration of plasma or whole blood. It is evidenced chiefly by a secondary anemia and a decreased blood volume, and may not be shown by the ordinary tests for hemoconcentration.

### Ununited Fractures

Nonunion of fractures is a frequent problem following projectile injuries. Such fractures require prolonged immobilization, and patience is often rewarded by bony union without more radical treatment. In the lower extremity, the use of a brace that protects the fracture but allows weight-bearing on the extremity is often productive of good results. If the nonunion is complicated by the presence of infection, the eradication of the focus with healing of the sinuses is a necessary preliminary step to surgical reconstruction, and may in certain cases be followed by healing of the fracture without other intervention.

The distinction between delayed union and nonunion is often difficult to make, and in many cases must depend on the surgeon's conviction of being able to offer the patient greater certainty of a good result and of saving time by proceeding with a bone-grafting operation at once. When the fragments are well aligned and in good contact, a minimal delay of six months appears to be wise, and the delay should be longer if bone infection has only recently been eradicated. In the case of the lower extremity, a trial of a weight-bearing brace should have been made.

In the case of malaligned or displaced fractures with nonunion, there is justification for earlier surgical intervention, since correction of the deformity is desirable and the chance of obtaining union by conservative methods is small. The same is true in cases with loss of bone substance in which natural healing cannot be expected to take place. In such cases the only cause for delay is a history of recent infection.

In the last war, it was a general rule to delay reconstructive surgery until at least six months after complete healing of the wound. Even this

period proved too short in many cases and latent infection flared up, causing failure of the operation. With the present availability of penicillin and the protection against infection that can be obtained by its use preceding and following operation, it seems unnecessary to wait for a period longer than three months when there is no clinical evidence of infection.

Loss of skin resulting in thin broad scars, particularly in the region of the tibia, frequently constitutes an obstacle to any operation on the bones. Generally it is the part of wisdom to turn such cases over to the plastic surgeon for excision of the scar and plastic repair, either by sliding or pedicle skin flaps, preliminary to attempts at bony reconstruction. This makes the task of reconstructive surgery easier and helps to ensure a good result.

So far as the operative procedure for overcoming nonunion is concerned, most orthopedic surgeons lean toward the on-lay graft, usually taken from the tibia, with fixation by metal screws of vitallium or stainless steel. The advantages of this procedure are that it obtains and maintains realignment of the fracture with rigid internal fixation and at the same time stimulates union through the application of the graft. When there is loss of bone substance, however, and a gap must be bridged by the graft, the results by this method have not been encouraging. After an apparently good result, at the end of three months with union of the graft there is generally a fracture through the graft and nonunion is re-established. This is thought to be due to a resorptive process in the graft that results from the fact that little if any of the transplant survives as living bone and that the larger part must be revascularized, resorbed and replaced by living bone before final union is obtained. The graft is weakened during the stage of revascularization, allowing fracture to occur with little or no violence.

Various methods of solving this problem have been tried. Those that have obtained the greatest measure of success are the double graft and, in the case of the tibia, the transplantation of the fibular shaft as a living bone graft. With the first of these methods double on-lay grafts are used and the space between the grafts is packed with chips of cancellous bone. There is increasing evidence that cancellous bone is more quickly revascularized and transformed into living bone than is cortical bone, and this procedure capitalizes on that observation. By the time the cortical grafts that maintain alignment and fixation are revascularized and weakened, there is every chance that the cancellous bone will have obtained union.

The fibula lends itself for use as a bone graft in the surgical repair of nonunion, because it can be spared without any functional loss, and also because it is a stout tubular bone and slowly undergoes revascularization and consequent weakening. In the case of nonunion of the tibia it may be used as a living transplant by means of transference first of one end and then of the other, without interference with the blood supply of the bone. By utilization of these newer methods, some of the extremities that were formerly sacrificed and amputated as a result of continued bad results may now be saved as functioning members. But to obtain good results in some of these cases, long-continued supervision and brace protection are required.

### Malunited Fractures

Although the level of fracture treatment is undoubtedly higher in this war than it was in the last, owing in considerable part to the higher standards of surgical training in recent years compared with those of twenty-five years ago, there are still a certain number of cases of complicated fractures that result in malunion. Although such results necessitate corrective operations, the matter of straightening a deformity of the long bones presents no great problem to the well trained orthopedic surgeon. If an open operation must be performed with an ostectomy, the modern trend is to employ internal fixation of a type that obtains rigid immobilization combined with excellent toleration by the tissues. This results in maintenance of alignment with the best assurance of rapid bony union and the shortest period of immobilization.

### Joint Injuries

Joint injuries resulting from war wounds are generally of three types. The first consists of the penetration of a projectile of some type into a joint with minimal intra-articular damage. The result depends on how soon and how thoroughly surgical treatment can be applied. If the patient can be treated with good facilities within six to eight hours, the foreign bodies can be removed, the joint washed out and closed and chemotherapy started. This generally results in avoidance of infection and restoration of satisfactory function without requiring reconstructive surgery. The second type of injury is one in which the projectile causes such extensive comminution of the bone that no matter how well it is treated in the early period, the damage is too great to offer possibility of functional restoration. The third type is one that is complicated by the development of infection, and regardless of the extent of the primary bony damage results in loss of articular cartilage and, from the functional standpoint, in limited or painful movement or both.

Reconstructive surgery is generally required in the latter two conditions, and the surgeon is faced with the difficulty of choosing between arthrodesis, which aims at obtaining solid ankylosis of the joint, and some type of arthroplasty aimed at retaining or restoring movement without pain.

In the last twenty years considerable experience with these different procedures has been obtained, which helps the surgeon to make this important

decision with greater certainty than before. In general it may be concluded that in the case of the wrist, shoulder or ankle, ankylosing operations in good position give better and more certain results than does arthroplasty. In the case of the elbow, good movement and function can be expected to result from resection or arthroplasty, the latter procedure being reserved for those cases in which the normal bony structure is preserved.

In the case of an injured knee or hip, the decision depends to a considerable extent on the wishes of the patient and his determination to obtain functional restoration, and also on the surgeon's experience and his conclusions concerning the relative merits of the two procedures. Excellent results have been obtained from arthroplasty of the hip and knee, but they are less predictable and certain than are those from arthrodesis. On the other hand, it can always be explained to the patient that arthroplasty does not burn his last bridge and that if the result proves unsatisfactory, arthrodesis may still be done. In general, however, when the function of the other joints is normal, better results can be expected from arthrodesis than from arthroplasty.

### Quadriceps Muscle Lengthening

One of the frequent complications of infected compound fractures of the femur following war injuries is fixation of the knee in extension. This is generally due to a combination of muscle damage and adherence of the quadriceps muscle to the femur, with loss of extensibility that prevents flexion of the knee. In 1919, Bennett[1] called attention to this condition and described a surgical procedure to lengthen the rectus tendon that resulted in restoration of function.

More recently Thompson[2] has described a new and simplified technic to obtain the same result. His procedure consists in isolating the rectus muscle and separating it from the vastus internus and externus muscle, and also from the intermedialis. When this is properly done, the knee can be flexed to an angle of 90° or better, and later by means of a program of exercise treatment excellent power of extension can be obtained. This may result in restoration of function in a knee that originally seemed hopelessly stiff.

### Nerve Injuries

Although nerve injuries are in the domain of the neurologic surgeon, they so frequently occur as accompaniments or complications of compound fractures that they also present problems for the orthopedic surgeon. Generally in such cases it is the best policy to clear up infection and obtain union of the fracture before attempting to repair the nerve. No neurologic surgeon is willing to mobilize and suture the nerve ends until wound healing has been obtained, and recovery of nerve function does not improve the condition of the patient until union of the fracture has been brought about. During this long period the paralyzed extremity must be supported by splints to prevent contracture of the normal unparalyzed muscles, and active and passive exercises should be carried out to maintain mobility of the joints.

Interesting studies on nerve repair have been made during this war, and these have resulted in the development of such new methods as the use of plasma glue and of tantalum wire and of the envelopment of the repaired nerve ends with tantalum foil, each of which is thought to represent an improvement on old methods. The value of nerve grafts, whether fresh or frozen, is still debatable, but the experience of this war ought to provide an answer to this question for all time.

Nor should it be overlooked that in case of failure to obtain repair of an injured radial nerve the orthopedic surgeon can offer an excellent substitute in the form of tendon transplantation, and also in the case of irreparable injury of the common peroneal nerve, in the form of arthrodesis of the subastragalar and midtarsal joints, with transplantation of the posterior tibial tendon to correct the drop-foot and varus deformity.

### Amputations

Although an amputation is always a mutilating operation, it may at times be a reconstructive procedure in that the artificial limb permits better function than would the crippled extremity. In most cases, however, an amputation is done as a life-saving procedure, and unfortunately in the treatment of war casualties it must frequently be resorted to. But the problem of future rehabilitation is intimately related to every amputation that is performed, and it is of the greatest importance to see to it that a stump is produced that is capable of wearing an artificial limb with comfort and of giving the patient maximal function.

As in the last war, amputations in the combat zone are being done by the guillotine method through the site of fracture, since this procedure saves the maximum length of stump and best deals with the problem of infection. The method requires continuous traction to the skin in the postoperative period. This is obtained through the application either of adhesive strips or of stockinette glued to the skin. When the operation is correctly done and the proper aftertreatment is employed, the results are astonishingly good. Healing generally occurs in six to eight weeks, complications are few, and many of the stumps, particularly in the case of the thigh and of the upper extremity, require no additional surgery. In the cases that have unsatisfactory and adherent scars, the secondary procedure is of minimal severity and consists of excision of the scar, mobilization of skin flaps and simple closure. Reamputation is required only in the case

of long below-knee stumps, and resection of bone only when there is infection.

Treatment of amputation stumps in this country is concentrated in seven Army general hospitals and in two Navy hospitals, which have been designated as amputation centers. Orthopedic surgeons who are especially experienced in amputation surgery and the fitting of artificial limbs are in charge of these services and direct the work. Limb-fitting shops have been set up in these hospitals, and as soon as the stumps are ready artificial limbs are fitted.

The Army is supplying articulated legs made of wood fiber that are readily modified to meet individual needs and are proving highly satisfactory. These will serve as alternate limbs when the veterans are fitted with permanent limbs after discharge from the Army. Special facilities have been organized to help in the rehabilitation of these patients.

## Rehabilitation

Finally, it should be pointed out that surgical reconstruction is only the first step along the path of recovery, and that a complete program of rehabilitation is required that ends only when the injured veteran has been replaced as a useful citizen in his community. Without this the finest surgery will fail to obtain satisfactory results.

Most of these men have undergone profound mental shock, and at the same time are confronted with social, family and economic problems that they feel unable to solve. They must be helped back to a healthy mental outlook, and here the services of a psychiatrist are necessary, helped by a competent social-service case worker who looks into the patient's family and social background and helps in solving the problems. Between them they help the patient to obtain a better social and psychologic readjustment.

A program of physical reconditioning is required to build up strength in injured and atrophied muscles and to restore movement in stiffened joints. This should begin when the patient is still in bed, and should aim both at restoring function in the extremities or parts of extremities that can be exercised and at awakening interest in an apathetic mind. Both doctor and nurse can play important roles in helping to develop and institute such programs as early as possible. Physical therapy and occupational therapy can play important roles in the program, especially after the patient has become ambulatory. At a later stage, gymnastics, sports, shopwork and a good recreational program can play their part in helping to achieve the maximum of physical reconstruction.

Finally, after discharge from the military forces, if the veteran's injuries are of a nature to constitute an obstacle to his returning to his former occupation, he should be given vocational training based on aptitude tests and vocational counseling. Such training should continue until the veteran has been placed on a job and has shown himself competent to hold it.

All these services are now available to the wounded veteran through the Army, Navy and Veterans Administration. If they are utilized to their fullest extent, the future fate of these men will be far better than after the last war and we may look forward with confidence to their return to their own communities and resumption of their places as useful citizens.

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## Discussion

Dr. Ezra Jones, Manchester: I want to express my appreciation to the author of this paper for taking up so many important points. His instructions about treating osteomyelitis by penicillin, without operative procedure, is extremely interesting. We have found that unless such lesions are open, with all the dead tissue cleaned out, the results are not particularly good. But with operative procedure and penicillin, they are excellent.

Dr. Robert R. Rix, Manchester: It is probably safe to say that the most frequent cause of delayed union and nonunion is the lack of complete, prolonged, adequate immobilization of the fracture. In some cases, I am sure that immobilization is stopped before it should be stopped and then the fracture is called nonunion when actually it is only delayed union. The immobilization should be complete. The unpadded cast should probably be used more than it is. The first cast, of course, should be lightly padded for reasons of circulation, but a skin-tight plaster can soon be applied to give complete immobilization. Also, if one immobilizes the fracture and permits early function, the chances of union are much greater than they are if the fracture is mobilized early. In other words early function and prolonged immobilization are preferable to early mobilization and short periods of fixation.

Dr. John Kopf (closing): I hope the impression has not been conveyed that we believe that these infections should be treated with penicillin alone and without surgery. Practically everyone agrees that where there is bone infection, with a sequestrum or actual infection in scarred areas, penicillin merely enables the surgeon to do a better job and does not eliminate the use of surgery. What we plan to do in most cases is to treat these patients with penicillin for a few days or a week and then operate to remove the sequestrums or the infected areas, with early secondary closure. No doubt we all agree with Dr. Jones that penicillin alone cannot be relied on to clear up these infections, except in acute cases.

Dr. Rix brought up the question of nonunion. Most of us will agree that lack of adequate immobilization is an important factor, but that is not the only thing; other factors come into the picture. We all know that fractures of the surgical neck of the humerus heal no matter what is done to them; no matter how much motion there is, one practically never sees a nonunion of the surgical neck. Mobilization is more desirable in those cases for function of the shoulder. In the tibia and the fibula, however, where there is need for adequate immobilization, I quite agree that if adequate fixation is not obtained, — and I am sure Dr. Wilson would agree with this, — either with a bone plate or some other fixation, a nonpadded plaster has an important place. We use it a great deal, and I find more and more orthopedic surgeons and general surgeons who having tried it are using it earlier and earlier.

A friend of mine recently saw me putting on a nonpadded plaster five days after the fracture, and remarked that he put them on in the beginning. He said that if he saw the patient within an hour or two after the fracture, he put the plaster on immediately after examination. But he admits that he would not do that after five or six hours or two days.

# MEDICAL PROGRESS

## THE PATHOGENESIS OF RENAL INSUFFICIENCY*

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IN POPULAR usage, the expression "renal insufficiency" has come simply to mean renal failure to maintain chemical homeostasis. In a restricted sense, however, there may be many renal insufficiencies. The acid-base balance may be maintained, while nitrogen accumulates in the blood, and conversely, nitrogen excretion may be unaltered when acidosis and dehydration result from urinary loss of water and electrolytes. Water reabsorption, nitrogen excretion or sodium conservation may each be affected individually, but in most disorders of renal function and structure, renal dysfunctions and their sequelae are multiple. The discussion that follows is devoted to a consideration of the pathologic mechanisms by which these disturbances are produced.

### DEFINITION OF UREMIA

In any discussion of renal insufficiency, the word "uremia" occurs again and again. Unfortunately, it lacks a final and widely accepted meaning, in large part because the growth of knowledge has wrought great changes in the concepts of renal disease. According to Fishberg,[1] the word was coined by Piorry in 1840 to designate the clinical state resulting from the "retention of urine in the blood." It is now recognized that losses of salt and water through the kidneys may contribute as heavily in the pathogenesis of the clinical syndrome as renal retention of metabolic waste products. Nonetheless, retention continues to be stressed in most authoritative definitions.[1–6] The clinical picture originally described has been shorn of those manifestations now known to be the effects of hypertension[1, 2] (hypertensive encephalopathy), although popular usage often overlooks this fact. Finally, minor differences in meaning appear among the various authoritative definitions, the following samples of which will suffice to illustrate the points of general agreement.

> "We characterize the clinical phenomena which occur exclusively with renal insufficiency as *true uremia*." Volhard.[6]

> "Uremia designates only that symptom-complex which occurs in conjunction with and as a result of the retention in the blood of urinary waste products." Harrison and Mason.[3]

> "Uremia — the symptom complex resulting from renal insufficiency and accompanying the retention of urinary constituents in the organism." Fishberg.[1]

> "Uremia — azotemia resulting from intrinsic renal disease." Goldring and Chasis.[4]

> "Uremia is the clinical syndrome which marks the point at which renal insufficiency is advanced enough to alter the composition of body fluids, with resultant serious disturbance of bodily functions." Page and Corcoran.[5]

Although it is generally conceded that the term "uremia" should be used only with reference to renal failure due to intrinsic renal disease, it is often extremely difficult or impossible to differentiate primary renal disease from disorders of the kidney secondary to extrarenal factors. Pure cases of either type are uncommon, since renal damage often causes changes elsewhere in the body that may in turn produce further destruction of renal tissue, whereas contrariwise, renal functional disorders produced by such extrarenal processes as congestive heart failure, traumatic shock and dehydration may provoke, if long maintained, serious and irreversible renal parenchymal lesions. Consequently, in this communication, the word "uremia" denotes the clinical state associated with nitrogen retention and disturbances of body water due to renal insufficiency, regardless of etiology.

### RENAL INSUFFICIENCY IN INTRINSIC RENAL DISEASE

Recent developments in the study of the renal structural and functional defects leading to insufficiency in chronic Bright's disease have been surveyed at length in a previous progress report.[7] The present discussion is concerned with certain special aspects of the problem.

#### *Glomerulotubular Imbalance*

Glomeruli and tubules vary considerably in size and probably, therefore, in functional capacity. Evidence has been advanced recently to support the view that a balance exists throughout the kidney between the glomeruli and tubules such that the capacity of one matches the capacity of the other.[8, 9] According to this concept, it is likely that in the normal kidney large glomeruli are attached to large tubules and small glomeruli to small tubules. With

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disease, this proportion is marred and the resulting imbalance appears to be responsible for many of the manifestations of renal insufficiency.[10] Thus, damage limited to the tubules results in an inability of the kidney to reabsorb efficiently the great volume of glomerular filtrate; body water and electrolytes are lost in large amounts, and death follows if restitutive processes, such as glomerular pressure reduction by afferent arteriolar constriction or by hypotension, do not come into action. On the other hand, impairment of glomerular filtration alone may result in oliguria and even anuria, since healthy tubular tissue may continue to operate blindly on the small volume of filtrate, concentrating it and reabsorbing solutes.

The last situation appears in the so-called "acute uremia" of organic renal diseases.[10] Here, glomerular damage causes a reduction in filtration rate. In view of the fact that most nitrogenous substances in the urine pass through the glomerular filter, it is not surprising that nitrogen retention follows filtration reduction. Urea, making up the largest moiety of the plasma nonprotein nitrogen, is particularly affected because it appears to diffuse back into the blood in large amounts when the urine flow is reduced and urinary concentration is increased. Sodium chloride and water are likewise retained because the tubule cells have an improved opportunity for reabsorption from the retarded stream of tubular urine.[10] Water and salt retention lead to edema and increased plasma volume.

Once glomerulotubular balance is restored in glomerulonephritis the clinical picture improves. If healing does not follow, however, imbalance may develop and produce the so-called "nephrotic syndrome." Although tubular damage is usually obvious histologically, the glomerulotubular imbalance in this instance is similar to that of acute diffuse glomerulonephritis, since water and salt retention appear. Glomerular damage in this state not only results in reduction of the filtration rate but also in the excessive loss of plasma protein. A general metabolic disturbance, manifested in hyperlipemia and hypercholesterolemia, may also be responsible for insufficient plasma-protein replacement.[11] Hypoproteinemia, with loss of water into the tissues, probably causes, in effect, a concentration of the plasma, setting in motion the hypophyseal-hypothalamic-renal mechanisms through which urine is concentrated. In this way further retention of water results. Moreover, urea is excreted in smaller amounts, as a consequence of oliguria and impaired filtration. With sufficient glomerular damage, azotemia may develop. In most cases of the nephrotic syndrome of chronic diffuse glomerulonephritis, nitrogen retention is not significant. In intercapillary glomerulosclerosis, on the other hand, the nephrotic syndrome and uremia frequently coexist.[12]

The renal insufficiencies that develop on the basis of the contracted kidney of chronic renal disease and of the extensive diffuse renal destruction of more acute disorders, such as malignant nephrosclerosis and bilateral cortical necrosis, are quite similar in their clinical manifestations and underlying renal functional patterns.[13] In all, tubular damage is severe. The remaining glomeruli may be attached to nearly nonfunctional tubes, which act simply as conduits for the passage of more or less unchanged glomerular filtrate to the bladder. The overburdened tubules become, as it were, "permanently diuretic": they are sufficiently active to remove glucose from the small total volume of filtrate but not capable of sparing water and electrolytes. Impairment of the "obligatory" water reabsorption is revealed in the approach of the urea and inulin clearances toward equality.[14] These factors play an important role in the production of hyposthenuria and isosthenuria.

*Hyposthenuria*

The formation of hypotonic or hypertonic urine requires renal tubular development and utilization of energy for osmotic work. Quantitative analysis of the relation between renal work and urinary concentration reveals that the renal tubular cells are called on to do a minimum of osmotic work when the urinary specific gravity is limited close to or fixed at 1.010.[15] When hyposthenuria develops in the course of renal disease, it is generally assumed that tubular damage prevents efficient energy development. Consequently, the determination of the maximal urinary specific gravity has been advocated as a measure of the extent of parenchymal destruction. Doubt has been cast on this concept. Goldring and Chasis[4] have observed normal urinary concentrating power in the midst of uremia due to malignant nephrosclerosis. Hyposthenuria frequently develops during shock at a time when no kidney damage is demonstrable. It is probable that other factors are concerned in establishing the maximal level of urinary specific gravity.

Hayman and his co-workers[16] have studied this problem carefully. They found that reduction of tubular tissue by any method was followed by hyposthenuria. When, however, the residual tubular tissue was obviously normal, as after subtotal nephrectomy, concentrated urine was formed if the glomerular pressure and filtration rate were lowered by hypotension or by increased plasma oncotic pressure (following the administration of acacia). When tubular damage was diffuse, as in uranium nephritis, these measures did not restore the concentrating power. This work indicates that a glomerulotubular imbalance may be responsible for certain cases of hyposthenuria. In these, the residual tubular transfer mechanisms may remain in good order, but the shortened time of contact between the cells and the tubular urine, as a result of nephron diuresis, may provide no opportunity for their operation. In short, a failure of energy utiliza-

tion rather than a deficiency of energy production is responsible. The possibility that this factor may be concerned in conditions of severe and diffuse tubular damage has not been eliminated. Under these circumstances, a great reduction of filtration rate would be required to permit efficient operation of the residual normal transfer mechanisms.

On the whole, Hayman's work supports the concept that the maximal urinary specific gravity and the residual functional mass of kidney tissue are related in diffuse renal disease. In this situation, the determination of concentrating power remains a valid and useful test. Corcoran and Page,[17] taking cognizance of the factors discussed above, have used the maximal specific gravity in devising an accurate clinical method of estimating tubular mass. According to these workers, the maximal specific gravity (S. G.) of the urine and the urea clearance (Cu), rough measures of glomerular filtration rate, are related as follows to the residual functional tubular mass (T), expressed in per cent:

$$\frac{(S.\,G.)-3.4}{2.58}\sqrt{Cu}=T.$$

It is properly emphasized that this formulation is approximative and may be invalidated by severe renal disease or extrarenal factors.

*Renal Reserve*

It is remarkable that renal disease must be far advanced before its presence is manifested by nitrogen retention. This apparent failure of a correlation between functional capacity and maintenance of homeostasis by the kidney has been ascribed to the operation of the so-called "renal reserve." There is considerable evidence in favor of this notion.[18] Underlying all discussions of reserve, however, is the assumption that intermittency of glomerular activity similar to that observed directly in the kidney of the frog[19] occurs in man. Direct[20] and indirect[9] evidence set forth in the past three years appears to have disproved this assumption. Other explanations must be sought for the phenomena previously ascribed to renal reserve. Much of the experimental work on dogs may be discounted because of trauma and anesthesia. In man, the lag in the development of azotemia as renal tissue is destroyed may be ascribed to two possible factors. First, protein intake is reduced by anorexia, a common symptom of chronic renal disease. Second, hyposthenuria and polyuria appear with progression of renal disease and result in more efficient excretion of urea. Of these alterations, the first is probably the more important since it has been shown that the blood-urea nitrogen concentration rises to a level commensurate with the urea clearance when urea is administered to patients with renal damage.[4] Changes of urine flow in man under various circumstances have frequently been ascribed to changes in the number of functioning glomeruli, that is, a shift in the size of the renal reserve. This explanation fails to take note of the fact that urine flow and glomerular filtration rate in man are not directly related. Urine flow may change through the widest possible range without any significant alteration in the rate of glomerular filtration. Moreover, it is gratuitous to seek a relation between the two in view of the extent to which filtrate volume exceeds urine volume. Sufficient evidence is at hand to support the view that urine flow is largely a function of tubular water reabsorption under the control of hypophyseal-hypothalamic humoral activity.

In many women who develop proteinuria and hypertension during pregnancy, signs of renal disease may clear completely during the puerperium. This syndrome may recur in subsequent pregnancies without permanent effect. It has been suggested that a congenitally small renal reserve may account for the clinical findings.[21] The stress of pregnancy is assumed to evoke increased renal activity, of which the kidneys are incapable. Proteinuria and hypertension are then thought to develop as a result of renal stress. Since the fundamental premise of this concept appears to be in error, however, it seems likelier that the "low-reserve kidney" signifies a benign form of the specific toxemia of pregnancy. Functional studies of the kidney in normal pregnancy have revealed no significant changes in renal blood flow, glomerular filtration rate, or tubular activity that might be construed as evidence of a strain imposed by pregnancy.[22] Indeed, it appears that pregnancy is not associated with detrimental renal functional change even when the kidneys have been damaged by essential hypertension or chronic diffuse glomerulonephritis, provided the specific toxemia of pregnancy does not supervene.[23]

## Renal Insufficiency in Extrarenal Disease

*General Considerations*

In a variety of illnesses, the signs and symptoms of renal insufficiency may appear in the absence of renal disease. The terms "prerenal azotemia" and "extrarenal uremia" have been applied to this state. In one respect these expressions are to be deplored because they divert attention from the kidney. It is true that extrarenal factors are primarily at fault and are to be dealt with therapeutically. Nonetheless, in the vast majority of cases, the renal dysfunction and damage are secondary and, in turn, cause nitrogen retention. In a small number, extrarenal factors of increased nitrogen intake or production give rise to azotemia.

The fundamental causes of impaired renal function in extrarenal uremia remain obscure, but recent work has thrown light on certain aspects of pathogenesis. Since peripheral circulatory collapse and dehydration are of common occurrence in all the conditions in which prerenal azotemia is seen, Fish-

berg[24] and others[25] claim that a renal circulatory defect lies at the bottom of most cases. Recent findings have strengthened their stand. The possibility remains, however, that alterations in plasma composition or nephrotoxins are responsible in many cases.

It has been widely held that hypochloremia may cause temporary, perhaps permanent, renal dysfunction. Hypochloremia is frequently associated with uremia, and it is difficult to produce uremia experimentally without reducing the plasma chloride concentration. It has been shown,[26] however, that hypochloremia may be induced in various ways without evidence of renal damage, provided plasma volume and osmotic pressure are sustained. Hiatt,[27] for example, succeeded in replacing as much as 70 per cent of the chloride ion by the nitrate ion, maintaining this state in dogs without ill effect for as long as three months.

It has been suggested that hyponatremia may be at fault because excess removal of the sodium ion always induces renal insufficiency.[28] Many studies have shown conclusively the vital relation between the sodium ion and the volume, hydrogen-ion concentration and osmotic pressure of the body fluids.[29–32] Since the kidney operates to maintain constancy of the composition of the plasma,[33] it is difficult to isolate the effect of salt depletion from that of dehydration. The balance between salt and water in the body, however, may be upset by low sodium intake, excess sweating and increased water intake. Under these circumstances, the chief phenomena referable to the loss of sodium are muscular spasm and slowed mentation.[30, 34] Nitrogen retention occurs as body water is lost under these circumstances, but the reduction in plasma volume and renal efficiency is held in check at a certain point beyond which marked hyponatremia must develop before further changes ensue.[30] It seems likely, therefore, that sodium loss per se cannot be implicated as the direct cause of renal functional change.

A complex series of reactions appears in response to the loss of body water and base. Fluid moves from the cells to the extracellular spaces, while the kidney excretes concentrated urine and operates selectively on the various electrolytes in the maintenance of normal plasma composition, often without regard for the total volume requirements of the body. Although the factors controlling plasma volume are far from clear, it appears that, so long as excess electrolyte loss is prevented, the volume is maintained relatively constant during water loss at the expense of the extravascular fluid[35]; but when sodium and other ions are depleted, plasma volume decreases and peripheral circulatory failure develops. Dehydration, however, cannot be thought of solely in terms of the volume of extracellular fluid. Hypertonicity of the blood has been shown to cause death in respiratory failure, probably as a result of marked cellular dehydration,[36] even when plasma volume is well maintained and circulation is adequate.[37] Under these circumstances, renal function is normal. When dehydration leads to a diminution both of the extracellular fluid and of the plasma volume, however, renal insufficiency becomes manifest, even before any evidence of shock is discernible.

The character of the demonstrable relation between dehydration, hypovolemia and impaired renal function is not clear. A reduction in renal blood flow and glomerular filtration rate as a result of active vasoconstriction has been found in such diverse states as orthostatic syncope,[38] chronic anemia,[39] traumatic shock[40] and Addison's disease,[41] all of which are similar, chiefly, in a reduction of the effective circulating plasma volume. Arterial hypotension is probably responsible in certain cases, but the phenomenon may be observed in the absence of blood-pressure change.[39, 41] The possibility of neurogenic mediation or of the action of humoral, endocrine or toxic agents cannot be entirely eliminated.

Toxins released by traumatic destruction of tissue, by the action of disease on the tissues or by microorganisms have been evoked at various times to account for the renal disturbances in extrarenal uremia. For the most part, the toxins in question have been purely hypothetical, their presence and action being posited on the basis of pathological findings, such as widespread focal necrotic lesions and renal tubular necrosis, after clinical manifestations of toxemia, such as high fever, prostration and coma. Certain specific agents have been implicated, however, particularly in traumatic shock and infection.

At this point it is necessary to consider how such toxins might affect renal function. It is often assumed that tubular damage by toxins is sufficient to account for azotemia and other manifestations of renal insufficiency, but this view is incomplete. If tubular dysfunction occurred alone, excess water and electrolytes might be lost, as in diabetes insipidus or Addison's disease, but the excretion of urea and most other substances would be unimpaired until changes in renal hemodynamics and filtration occurred. Hence, any view of extrarenal uremia as secondary to toxic renal damage must include interference with glomerular filtration in an important position. Tubular lesions contribute to the total picture but alone cannot produce it. A possible exception to this point of view is found in conditions in which toxic agents, such as mercury, uranium, sulfonamides and possibly "heme" pigments, are concentrated to dangerous levels in the tubular urine. Even here, however, it is interference with filtration by blockage of the tubules, by total nephron destruction or by other mechanisms that leads ultimately to nitrogen retention and uremia.

Disorganization of renal functional activities is a constant factor in all the conditions to be discussed

below. The considerations set forth above with respect to glomerulotubular imbalance in intrinsic renal disease hold force here. Impairment of filtration rate greater than that of tubular function may lead to the excretion of a highly concentrated urine in small amounts. In most cases, however, tubular dysfunction appears to be profound and a dilute acid urine is formed, often in normal daily volumes. Since the urine is derived from a greatly decreased filtration bed, nitrogen excretion remains impaired despite the normal or even high urine flow. Hyposthenuria under these circumstances, however, may not necessarily indicate tubular damage. If the over-all filtration rate is reduced as a result of complete cessation of activity in a sufficient number of glomeruli, hyperfiltration in the remaining functional units may result in the formation of dilute urine.

*Peripheral Circulatory Collapse*

It is well known that shock following trauma, blood loss, burns and the like is associated with a serious derangement of renal function manifested in oliguria or anuria, excretion of a dilute acid urine and nitrogen retention. It is less well known that this disorder of renal function may persist even after recovery from shock, ultimately leading to death in uremia. Cases such as those reported by Husfeldt and Bjering,[42] by Darmady and his co-workers[43] and others[44–46] are unusual in civilian practice. In combat areas, so-called "traumatic uremia" has been seen more frequently both because shock is frequent and severe and because treatment is often delayed. Darmady et al.[43] found that one third of their fatalities at an air-evacuation hospital in England were of this nature. Six severely injured men in whom crushing injury was not a factor died in uremia four to seventeen days after injury and recovery from shock.

The renal pathology of traumatic uremia varies remarkably from minimal cloudy swelling of the tubular cells, to extensive bilateral cortical necrosis.[42, 43, 47, 48] In general, the kidneys are enlarged and edematous. The glomeruli may be bloodless or show changes resembling those of acute diffuse glomerulonephritis.[42] Degenerative changes of the tubular cells are usually prominent. These lesions range from lipoidol infiltration to necrosis. There may be focal nephron destruction, tubular blockage by casts or tubular disruption. As a rule, the pathological picture is best described as a nephrosis.

Renal function during traumatic, burn and hemorrhagic shock in man[40] and animals[49, 50] has been studied intensively in recent years as a result of the stimulus of war. In the dog, episodes of hemorrhage sufficient to produce hypotension are at first easily reversible by transfusion but, if repeated frequently and quickly enough, lead to irreversible shock.[49] Renal blood flow, also, is at first easily returned to a normal level by transfusion, but after the second or third bleeding, undergoes protracted reduction and fails to recover after transfusion. This phenomenon precedes the development of irreversible peripheral circulatory collapse. In man, renal blood flow is nearly always markedly decreased during shock.[40] Transfusion results in prompt recovery of blood pressure and cardiac output in most cases, but the renal circulation does not improve proportionately owing to active vasoconstriction within the kidney. A similar vasoconstrictive response in dogs occurs even when the kidney is denervated or is under the influence of a sympathicolytic agent (933F).[49] These facts indicate that a vasoconstrictive humoral agent that does not act on the sympathetic nervous system may be responsible. It has been suggested that increased renin production occurs in shock,[51, 52] perhaps as a defense measure, but the only vasoconstrictor substance Page[53] could find in the blood of shocked animals did not behave like angiotonin. Indeed, it appears that the vascular system becomes refractory to angiotonin following hemorrhage or extensive central nervous system trauma.[53] Other workers[54] have also failed to find evidence that the renal pressor system is active in shock.

Since approximately 25 per cent of the cardiac output pours into the kidney normally,[38] renal vasoconstriction during shock effectively diverts a significant mass of blood to more vital organs. A similar buffering circulatory activity of the kidney has been found normally present and highly developed in certain animals. The seal, for example, can endure long periods of asphyxia during diving, in part because blood is diverted to the heart and brain from the kidney by intense vasoconstriction.[55] In man, it may be that a similar normal activity of the kidney (if maintained too long by shock) is detrimental and irreversible. Penner and Bernheim[47] have shown that intense renal vasoconstriction, if sufficiently prolonged, causes bilateral cortical necrosis, a disorder they and others[48] have observed following shock.

On the other hand, vasoconstrictive toxins released from traumatized tissues may be at fault in evoking a pathologic response. The hypothesis that the entire shock state is produced by circulating toxins has long had wide support.[56] At the close of World War I, this hypothesis was generally held to be well founded as a result of the extensive work of Cannon[57] and others. Subsequent work[58] has discredited certain of the major premises of the toxemia theory,[58] and the view that the reduced plasma volume of shock is secondary to local fluid loss rather than to a generalized loss through toxin-damaged capillaries has gained strength. Facts have emerged recently, however, that appear to give some weight to the toxemia theory. A number of workers[59–62] have shown that a toxic substance may appear in lymph draining from crushed or traumatized regions or in the blood during circulatory collapse. Moreover, it has been claimed that bacterial toxins arising from anaerobic bacterial growth in macerated tissues

may be responsible.[63, 64] Although the latter finding casts doubt on the validity of much of the evidence for a toxin in muscle extracts, there is good reason to believe that pigments and possibly other substances released from damaged muscular tissue may be responsible for the profound renal damage of the "crush syndrome."

In 1941, Bywaters and Beall[65] described the "crush syndrome," observed following prolonged compression and crushing of muscles in victims of the air war over London in the fall of 1940. Their observations have been repeatedly confirmed, and a large number of additional cases have been reported. Severe shock apparently always develops after such an injury and usually responds to treatment. Following recovery from shock, clinical evidence of renal insufficiency appears and death in uremia occurs in about eight days. Myohemoglobin and creatine appear in the urine in large amounts shortly after release of the compressed part, and it has been suggested that myohemoglobin may have a nephrotoxic action.[66] Pathologically, the renal lesion resembles that of shock. The tubules are markedly damaged. Necrosis with fragmentation and blockage by brown granular casts are particularly prominent in the distal segments.[66] The casts appear to be precipitated myohemoglobin.[67] Other states in which "heme" pigments are free in the blood, such as blackwater fever,[68] transfusion reactions[69] and spontaneous myohemoglobinuria,[70] may also be complicated by renal failure. A similar lesion has been produced in acidotic dogs with canine methemoglobin.[71] Bywaters and Stead,[72] also, found acidosis requisite for the production of tubular lesions in rabbits with human myohemoglobin. It is unlikely that methemoglobin is involved in man, since this substance may occur free in the blood without effect[73] and does not appear in the urine of patients with traumatic shock or the crush syndrome.[71] Whether shock is necessary in the production of the crush syndrome in man is not clear.

*(To be concluded)*

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31431

#### PRESENTATION OF CASE

A thirty-five-year-old woman entered the hospital complaining of a limp in the right leg.

Eight months before admission, while walking downstairs, she felt her right hip suddenly give way simultaneously with a sensation of numbness and tingling in the right heel. During the following night a black-and-blue area developed on the posterior aspect of the thigh, spreading downward to the midcalf. There was no pain at any time. At a community hospital she was placed in a spica. After eight weeks the cast was removed and the patient walked with crutches. Limitation of flexion of the right knee was noticed for the first time. A month later she began to walk without crutches. There was no pain in the hip, but the right leg remained swollen and heavy, and she limped.

Twelve years before admission the patient was exposed to syphilis but noted no primary or secondary lesions. Ten years later she had a blood test and was then given weekly hip injections for two and a half years. There was no history of headache, vertigo, paresthesia, shooting pains or visual disturbance.

Physical examination revealed a well developed and well nourished woman in no distress. The pupils were irregular, the right being slightly larger than the left and reacting less to light than the left; both reacted to accommodation. The heart and lungs were negative. The right lower extremity was 2.5 cm. shorter than the left. The right upper thigh was firm and swollen. The right hip showed a permanent flexion of 50°, but further flexion to 80° was possible. The extremity was externally rotated. There was no internal rotation of the thigh on flexion or extension. External rotation was 30° on flexion. Abduction was 25°. Extension of the knee was normal. Flexion of the knee was possible to 150°, with painless catching. The left patellar and Achilles tendon reflexes were slightly hyperactive; those on the right were present and normal. There was no clonus or Babinski sign. Position sense was normal. The visual fields were normal.

The blood pressure was 135 systolic, 85 diastolic. The temperature was 99°F., the pulse 80, and the respirations 20.

Examination of the blood revealed a red-cell count of 4,750,000, with 80 per cent hemoglobin, and a white-cell count of 15,000, with 68 per cent neutrophils. The urine gave a + test for albumin, and the sediment contained 25 red cells and 10 white cells per high-power field. The serum calcium was 9.6 mg. per 100 cc., the phosphorus 2.9 mg., and the alkaline phosphatase 8.5 units. Blood Hinton and Wassermann reactions were positive. The spinal-

*On leave of absence.

fluid Wassermann was negative, as was the gold-sol curve. The spinal-fluid protein was 22 mg. per 100 cc.

An x-ray film of the chest revealed no lesions in the lung or bones. The right knee showed decalcification of the bones, but the joint appeared normal. The right thigh showed a transverse fracture of the neck of the femur (Fig. 1). The greater trochanter was displaced upward and somewhat laterally. A large laminated, calcific mass, irregular in outline, surrounded the lower neck and the upper half of the shaft. The mass was somewhat less calcified in the region immediately adjacent to the shaft and in the region of and distal to the trochanter. The outline of the femur was irregular and somewhat moth-eaten, and there were multiple areas of decalcification in its substance. The periosteum was lifted for some distance below this large calcific mass.

An operation was performed.

FIGURE 1. *Roentgenogram of the Right Hip Taken Eight Months after the Initial Injury.*

## DIFFERENTIAL DIAGNOSIS

DR. CHANNING C. SIMMONS: We might as well see the x-ray films first.

DR. CLAYTON H. HALE: These films, taken at the community hospital at the time of injury, show fragmentation of the upper end of the femur, with fracture through the base of the neck and the greater trochanter, and there is this calcified density surrounding it (Fig. 2). Surely, it makes one think of a pathologic fracture, and it is difficult to tell just what this material is. One suspects that it is calcification in a hematoma, but I assume these films were taken

right after the accident, and there would not have been time to lay down that amount of calcium. These later films were taken here, and they show considerably more of this calcified material lying out in the soft tissue; they suggest the appearance of nonunion, which one might also see with pathologic fracture. The density is well rounded off in this area, and one surely must think of a Charcot joint.

DR. SIMMONS: But you would expect it to be more in the joint, would you not?

DR. HALE: Yes; that is the usual thing.

These films were taken after the patient came here. The material in the soft tissue has become organized and shows an attempt at early bone formation. You can see periosteal calcification here, and evidence of metallic material in the buttock.

DR. SIMMONS: The discussion of any of these bone diseases comes down to a consideration of conditions under three headings: general systemic disease, such as tuberculosis and syphilis; skeletal disease, such as osteitis fibrosa cystica and Paget's disease; and bone tumors, benign and malignant, primary and metastatic.

Regarding systemic diseases, what data we have rule out tuberculosis. Syphilis always has to be considered. This is not a typical Charcot joint because it is not in the joint, and it is not the characteristic picture of syphilis of the bone. I do not believe, however, that there is a characteristic picture of syphilis of bone. There is the one that is most frequently seen, but about anything can be observed.

The systemic disease to consider here is Paget's disease. The patient was rather young for that — thirty-five years. We have no other films of bones with which to compare these films, but there is nothing to suggest Paget's disease; nor is there anything to suggest osteitis fibrosa cystica.

We are left with the consideration of some form of bone tumor or a traumatic condition, keeping the reservation of possible syphilis. The patient presumably had a pathologic fracture; that is, the leg collapsed while she was going downstairs. Spontaneous fracture of the neck of the femur may occur in an elderly person, but one would hardly expect it to occur in a person of thirty-five; therefore, a pathologic fracture seems likely. None of the films taken at the time of injury are satisfactory (Fig. 2). All are rather hazy, but one can see some bone formation around the area. The joint looks normal. I do not know exactly how soon after the accident the films were taken, but one would not expect, as Dr. Hale has said, to see new-bone formation in the hematoma. There is also definite evidence of a progressive condition.

I believe that this is probably some form of bone tumor. We have nothing to suggest that she had a primary lesion elsewhere, except possibly the albumin and few red cells and pus in the urine, which, of course, might have come from the bladder or from a vaginal discharge. There is no record of an examination of the abdomen, so we do not know whether she had a primary tumor of the kidney with metastases to the bone, the metastases having given the first symptoms. The blood examination is informative, since the phosphorus and calcium were normal and the phosphatase was elevated. One expects an elevated phosphatase in any process in which there is as much new-bone formation as there was here. An organizing hematoma raises the phosphatase. An osteogenic sarcoma also raises it,

FIGURE 2. *Roentgenogram of the Right Hip Taken at the Time of Injury.*

whereas a Ewing's tumor rarely has any effect. The serum protein level is not given, but in plasma-cell myeloma the serum protein is usually elevated. Plasma-cell myeloma, however, is a bone-destructive lesion, and there is nothing in the x-ray films to suggest that. Of the primary tumors of bone, benign and malignant, the malignant ones usually come at a somewhat earlier age than this; but any tumor, with the possible exception of chondroma or chondrosarcoma, which I prefer to call osteogenic sarcoma of the chondral type, is often found in people of sixty to seventy.

These first films do not show much. The patient obviously had something that weakened the bone. She could have had a chondroma of the bone that weakened it and caused it to collapse, with new-

bone formation. I believe that an osteochondrosarcoma is the most plausible diagnosis in this case, always reserving syphilis. There is irregular bone formation, and in this, there is ray formation of bone, which is probably coming down under the periosteum, with new-bone formation and bone destruction at the same time. It is difficult to say whether tumor is superimposed over the neck of the femur. An osteochondrosarcoma, if you want to call it that, is a low-grade sarcoma; if treated relatively early, it can usually be cured by total removal. It is not a radiosensitive tumor.

Dr. David Williams: The operation was a biopsy. There were ray formation and new bone in the lateral and lower aspects of the mass, as one would expect from the x-ray. There was nothing else remarkable, and we had no other clue.

Dr. Ronald C. Sniffen: Do you know the opinion of the other members of the service?

Dr. Williams: We were all completely at sea.

## Clinical Diagnosis

Tumor of femur?

## Dr. Simmons's Diagnosis

Osteochondroma or osteogenic sarcoma (chondral type) of relatively low malignancy.

## Anatomical Diagnosis

**Multiple cysts of femur?**
**Excessive callous formation?**

## Pathological Discussion

Dr. Sniffen: My remarks on this case are a little anticlimactic. The biopsy consisted of a generous fragment of the calcific mass and a layer of overlying soft tissue. The mass consisted of bone trabeculae with pronounced osteoblastic activity in some areas and minimal activity in others. Osteoclasts were also present, but in relatively small numbers. The intertrabecular spaces contained a few fibroblasts and small groups of fat cells but were occupied for the most part by innumerable channels of varying diameter. Some of these were obviously blood vessels, but the majority contained fluid and granular precipitate, and their walls seemed to consist of a fine membrane of connective tissue without an endothelial lining (Fig. 3). This is reminiscent of what is seen in the cortical shell of a solitary bone cyst. In the layer of overlying soft tissue there was a surprising degree of endarteritis.

Figure 3. *A Photomicrograph of the Calcific Mass, Showing the Bone Trabeculae and the Cystic Spaces.*

We cannot make a diagnosis, but if it is presumed that this biopsy is representative of the mass as a whole, various conditions can be ruled out, such as malignant tumor, giant-cell tumor, fibrous dysplasia and osteomyelitis. There was no evidence of syphilis, and I can find no reference to such changes in a Charcot joint, either in the pre-ataxic stage or in the ataxic stage. There was no indication of an organizing hematoma. Perhaps the process is merely excessive callous formation.

In spite of our dilemma the patient is well. She has no pain and is walking without aid. It is now ten months after the fracture.

## CASE 31432

### Presentation of Case

A fifteen-year-old boy entered the hospital complaining of pain in the left biceps muscle.

After an attack of scarlet fever three years before admission, he noted the gradual development of intermittent stabbing pain in the left biceps muscle, made worse by use of the muscle. There was occasional radiation of pain and numbness to the left hand. A year before admission weakness of the left arm appeared and progressed, and the muscle pain became extremely severe.

The past history was noncontributory.

Physical examination revealed a well developed and well nourished boy. The heart and lungs were normal. The spine showed left dorsal scoliosis, with winging of the scapulas. The left arm was atrophic and weak, especially about the elbow, with weakness also of the wrist and hand. The left triceps and radial reflexes were weaker than those in the right, and the left biceps reflex was questionable. The left biceps muscle was tender. When its strength was being tested by pull against it, the patient complained of pain in the muscle, which radiated down the ventral aspect of the forearm into all the fingers. During an attack of such pain an area of hypesthesia to pinprick appeared in the medial portion of the volar aspect of the left forearm. This lack of sensation lasted a short time, and in the absence of pain, hypesthesia was also absent. The skin of the left hand was more wrinkled and moist than that of the right. On electromyography, the only abnormal finding was hyperirritability of the extensor carpi radialis.

The temperature was 98.6°F., the pulse 70, and the respirations 15. The blood pressure was 125 systolic, 75 diastolic.

Examination of the blood revealed a hemoglobin of 12.8 gm. and a white-cell count of 8200, with 68 per cent neutrophils. The urine was normal. The blood chemical and spinal-fluid findings were negative. An x-ray film of the left shoulder region showed loss of the lordotic curve of the cervical spine, with evidence of spur formation about the margins of the vertebras. The joint spaces were of normal width. The visualized bones about the left shoulder joint and the proximal portion of the humerus were normal. In the distal third of the humerus there was widening of the cortex in its medial portion, with a somewhat irregular and indefinite area of increased density, as well as central rarefaction extending out from the medullary canal (Fig. 1).

An operation was performed.

### Differential Diagnosis

Dr. Carroll B. Larson: This is a good example of how a great number of facts regarding a history and examination are put together without following any of them to their actual termination, so that they have some value. All sorts of conditions are suggested by the history, both neurologic and orthopedic. For example, although the record does not definitely say so, some of the neurologic findings suggest that there may have been injury to the cervical spine, yet it does not tell what the motions of the cervical spine were, to help rule it in or out.

Figure 1. *Roentgenogram of the Humerus, Showing the Area of Rarefaction Surrounded by Dense New-Bone Formation.*

Another point of interest is the tender biceps muscle. A muscle can be tender in many ways. If you push from front to back on the biceps muscle, you may be eliciting tenderness on the underlying bone, but if you squeeze the muscle and find that it is tender, it means something entirely different. It is an important point.

The neurologic points registered here involve components of both the radial and ulnar nerves, and if one went into the realm of peripheral nerve lesions, one would have to consider lesions involving more

than one nerve simultaneously, and roots at more than one level. All in all I think that the history and examination are of little help in trying to establish a diagnosis. Take an isolated fact, that of tenderness in the biceps muscle, and assume that the pressure was from front to back, which is the most frequent way in which tenderness is tested. If that was true, it might have elicited tenderness in the underlying bone. Or, by using the biceps muscle along with the brachial muscles, because they go together, the patient may have been pulling on some sensitive periosteal attachments overlying a bone lesion. We know perfectly well that in bone disease many vague patterns of nerve distribution pain may be elicited. They defy explanation of how they occur, whether reflexly or otherwise. Because this is a vague story of nerve distribution, one might conjecture that the lesion was in the shaft of the humerus, and that the pain elicited was from muscle pull on the sensitive area.

May we see the x-ray films?

Dr. Clayton H. Hale: These films show the marked cortical thickening and the central area of rarefaction that were described. The latter looks almost like two cystic areas. I cannot make out any soft-tissue mass. One must think of a chronic low-grade inflammatory process as the likeliest diagnosis from the x-ray point of view.

Dr. Larson: There is a definite area of decreased density in the middle of a very dense orderly arrangement of periosteal new-bone formation. This x-ray appearance, disregarding the clinical points entirely, strongly suggests three possibilities — cortical abscess of bone, Garré's sclerosing osteomyelitis and osteoid osteoma. Garré's osteomyelitis, however, can be eliminated, because there is no focal point in this condition. Furthermore, Garré's disease usually involves the entire circumference of the shaft. For a cortical bone abscess, this, again, is not a characteristic x-ray picture, because when there is irritation from a point of infection in bone, one is apt to observe surrounding density as much on one side of the abscess as on the other. The area of decreased density lies next to the medullary cavity, and on that side there is little new-bone formation, except for a shell. In cortical abscess of bone I should expect the bone reaction to be more symmetrically divided on both sides of the lesion than it is here. This obviously has been going on a long time, because of the orderly arrangement of the periosteal new bone. One would not expect it to be a rapidly growing tumor, for in such cases there is a disorderly arrangement of bone formation.

The third possibility, which is by far the strongest, is that of osteoid osteoma. The cause of osteoid osteoma, whether infection or true tumor, is unknown, but regardless of that, this presents what we consider to be the characteristic x-ray picture of osteoid osteoma, that is, an orderly arrangement of periosteal new-bone formation, which is more or less a reaction to a foreign substance, whether it be tumor or infection. Reaction is likelier to occur on the periosteal side of the bone, with only little reaction of the medullary side. This fits the picture of osteoid osteoma extremely well. I should have liked to know from the history more about the character of the pain. A severe deep bone ache is almost typical of osteoid osteoma. Furthermore, I should also have liked to know whether direct bone pressure on the lesion by the examining finger produced pain, because pressure over one of these areas intensifies the original pain. If that had been noted, one could suspect that diagnosis on the clinical aspect without waiting for the x-ray studies. I believe that this was probably an osteoid osteoma.

Dr. Earl Glendy: What about the x-ray films of the cervical spine that are recorded as showing evidence of spur formation at the margins of the vertebras? Is that not unusual for a boy of fifteen years?

Dr. Hale: The only film that we have is an anteroposterior one that does not show the spurs mentioned in the report. I can see nothing abnormal on this film. I am sure there were other films.

Dr. Channing C. Simmons: The possibility of syphilis always has to be considered. I do not believe it is syphilis, but because of the thickened periosteum of the bone one should keep it in mind.

Dr. Ronald C. Sniffen: What was your impression at operation, Dr. Williams?

Dr. David Williams: We did not know what it was. We thought that it might have been an osteoid osteoma because of the swelling. It was difficult to find the area of rarefaction. There was no pus. There was a definite cavity containing granular crumbling bone, which was weaker than the surrounding bone. The cortex was quite brittle, more than one might normally expect. A culture was taken from the area, and it was cleaned out; nothing further was done.

Dr. Simmons: Were the symptoms relieved?

Dr. Williams: The boy has been completely relieved and was discharged five weeks after operation. We have seen him once since then.

### Clinical Diagnosis

Osteoid osteoma of humerus?

### Dr. Larson's Diagnosis

Osteoid osteoma of humerus.

### Anatomical Diagnosis

**Osteoid osteoma of humerus.**

### Pathological Discussion

Dr. Sniffen: Microscopic sections of the lesion showed fragments of extremely cellular, vascular connective tissue, and in this, osteoid trabeculae

were embedded (Fig. 2). These trabeculae were lined by osteoblasts and occasional osteoclasts. The trabeculae of the adjacent spongy bone were thickened, and the marrow fibrous. There was no inflammatory infiltration or evidence of degeneration.

important to know where it is, because you will not cure the patient unless it is removed. By varying the x-ray technic in spot films, you may be able to demonstrate the nidus. This is the same bone with a variation in the technic; it shows where the nidus

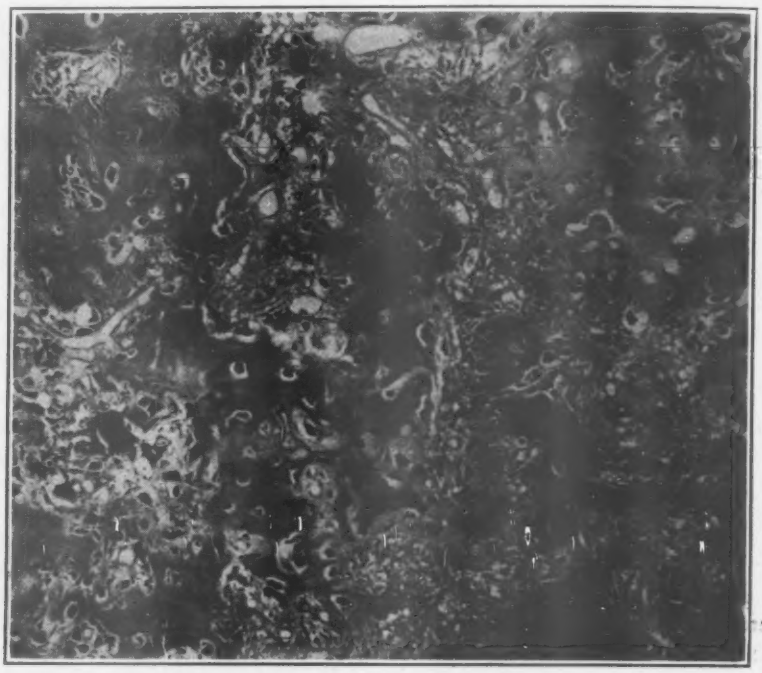

FIGURE 2. *Photomicrograph of the Lesion of the Humerus.*
*Note the trabeculae of calcifying osteoid tissue embedded in a cellular and vascular connective tissue, as well as the osteoblastic activity and the few osteoclasts.*

Our diagnosis was osteoid osteoma. The culture showed no growth.

DR. ARTHUR L. WATKINS: Do these recur, Dr. Larson?

DR. LARSON: As a rule, they do not. In 1935, Jaffe[1] first described this lesion by reporting a series of cases; in 1940, he and Lichtenstein[2] published a follow-up and noted no recurrences in any of them.

There is one important point about examining these people radiographically. I think that I can demonstrate this by showing some slides. This is a routine x-ray picture, in which you do not see the nidus. If you suspect that a nidus is present, it is

is so that it can be removed surgically. This is the same lesion after removal, and you can see the nidus in the gross specimen. The bone you have to go through, as Dr. Williams has pointed out, is extremely sclerotic.

DR. SNIFFEN: These lesions, although first consisting of trabeculae of osteoid tissue, gradually calcify and thus become more radio-opaque.

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## BACK TO THE OLD JOB

The private practice of some 40,000 physicians who joined their country's forces during the past four years has, in a sense, been held in trust for them by those who stayed at home. These physicians have as much right to return to their old jobs, so far as such a thing is possible, as have the GI's whose jobs have been guaranteed them by force of public opinion. The difference is that the practitioner's job has been created by himself, over a period of years, and can be guaranteed to him only by the loyalty of his patients and the good faith of his colleagues who have been carrying on for him in his absence.

That the home-guard physician has a clear-cut responsibility in the matter is suggested by the experience of a respected and capable pediatrician, returning after four years of military service, during which he was officially recognized for his devotion to duty; a colleague (or competitor) who had cared for some part of his practice in his absence was reported to have warned a patient, more or less directly, that three years in a fox hole had in no way contributed to her former doctor's capacity to reenter the practice of pediatrics.

A people whose freedom has been preserved by a considerable effort on the part of several million of their countrymen certainly cannot be taken for bondsmen. They can be thought of only as free agents in their choice of physicians, regardless of any legislative rumbling to the contrary; they are not marked or branded; they are part of any practitioner's following only so long as he has the skill or personality to hold them. Any stay-at-home doctor who has benefited by the absence of another is in duty bound, however, to suggest to his colleague's patients not only that they are free to return to their former fold but that the decent thing would be for them to go there. Beyond that he is free unless he had entered into an agreement with his colleague to care for these patients for the duration only.

There must, as a matter of fact, be comparatively few of the remaining civilian doctors of merit who are interested in carrying their excess baggage any longer than is necessary. A considerable percentage of the survivors being fifty or more years of age, they may well be weary of too constant a struggle against bifocalism, of wrestling with the problems of nonavailable hospital rooms and absent nurses and of constantly dredging in the muddied channels of their memories for names that refuse to affix themselves to faces. They also know the weariness of war, even in its home-front aspects.

## EPIDEMIC DIARRHEA OF THE NEWBORN

The July issue of the *Quarterly Bulletin* of the Department of Health, City of New York, called attention to the increased number of outbreaks of epidemic diarrhea of the newborn that were re-

ported in 1944. There were thirty-one such outbreaks, the highest on record, surpassing 1943 by eleven, with a morbidity rate for those exposed of 18.8 per cent, and a case fatality rate of 30.1 per cent — a dangerous disease indeed.

The first outbreaks of epidemic diarrhea of the newborn were observed in the early 1930's and were summarized in 1937 in a paper read at the Pediatric Section of the American Medical Association by Rice, Best, Frant and Abramson.[1] In one of these which occurred in New York City, there were 32 deaths. Many other reports have appeared in both American and foreign literature since that time, the disease now being recognized as a clear-cut entity, occurring sporadically in the nurseries of lying-in or general hospitals. In the eleven years ending with 1944, New York City alone, according to the *Bulletin*, had one hundred and thirty-six such outbreaks, with 800 deaths and a case fatality rate of 34.8 per cent.

The infection, occurring during the newborn period of life, usually in the first week, is characterized by frequent, yellowish or greenish, watery stools, rarely containing blood or pus and by rapid distention, marked dehydration and acidosis. Terminal pneumonia may appear, but otherwise few complications present themselves and little change in temperature is observed. Death is due to the extreme dehydration and intoxication. Treatment, as is usual for such conditions, consists of starvation and the intravenous replacement of fluids.

In recent years, a number of outbreaks of epidemic diarrhea of the newborn have been reported in Massachusetts[2] and probably others have occurred. In New York City the simple occurrence of diarrhea, unclassified and undefined, in a newborn nursery during the first three weeks of life is reportable. In view of the seriousness of the disease and its recent rise in incidence elsewhere, it seems likely that a similar regulation should be adopted by the Massachusetts Department of Public Health.

The very fact of the gathering together of newborn infants in nurseries is not without its dangers, and these risks should be constantly borne in mind by those in authority, and constantly guarded against.

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2. Personal communication, Division of Communicable Diseases, Massachusetts Department of Public Health.

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATHS

HOYT — Park R. Hoyt, M.D., of Laconia, died August 31. He was in his sixty-fourth year.

Dr. Hoyt received his degree from Dartmouth Medical School in 1906. He served in the Medical Corps in World War I.

McLAUGHLIN — Patrick J. McLaughlin, M.D., of Nashua, died September 8. He was in his sixty-seventh year.

Dr. McLaughlin received his degree from Baltimore Medical College in 1906.

WILDER — Richard E. Wilder, M.D., of Whitefield, died August 24. He was in his seventy-sixth year.

Dr. Wilder received his degree from Bellevue Hospital Medical College in 1894. He was a past president of the New Hampshire Medical Society.

His widow, two sons and a daughter survive.

## MISCELLANY

### DDT CONTROL INFORMATION DEVELOPED BY GOVERNMENT AGENCIES

Release of DDT for public use and its consequent widespread sale for industrial and household purposes have been arousing interest in industrial hygienists throughout the Nation, as reflected in inquiries recently received by the Industrial Hygiene Division, United States Public Health Service.

Caution labels for commercial containers of DDT have been formulated, in accordance with the Federal Insecticide Act, and are expected to be in general use soon. A leaflet setting forth the labeling provisions may be obtained from W. G. Reed, chief of the Livestock Branch, Production and Marketing Administration, United States Department of Agriculture.

The Industrial Hygiene Research Laboratory of the Public Health Service is maintaining close contact with companies manufacturing DDT, studying the hazards associated with its production, handling and use. Before the Army's release of the insecticide for field use by its personnel, extensive tests of biologic effects were made by this laboratory. No case of poisoning actually due to DDT has occurred in the United States, reports the chief of the laboratory. In more than two million persons exposed to DDT in its use by the Army for control of insect-borne diseases, no case of poisoning is known to have occurred.

Those cases of toxicity that have occurred to the present time have been due to the solvents used in the DDT mixture. Many of these solvents, such as kerosene, xylene and others, in themselves may cause irritation of the skin and other harmful systemic effects when handled carelessly. Such effects may be avoided by observing proper precautions and strict personal cleanliness. It is recommended that the chlorinated hydrocarbons, with the possible exception of methylene chloride and trichlorethylene, should not be used as solvents for DDT.

In the manufacture of DDT and its products, where workers will be exposed to the substance daily for a period of years, certain precautionary measures are recommended. These are set forth in a pamphlet *DDT Toxicity: A report on*

*the toxicity to warm-blooded animals of aerosols, mists and dusting powders containing DDT*, which may be obtained from the Industrial Hygiene Research Laboratories, National Institute of Health, Bethesda 14, Maryland.

Many bulletins and articles have been published by this laboratory and the Division of Physiology of the National Institute of Health, exploring the effects of DDT on man and various warm-blooded animals. These may be obtained from the Public Health Service. Questions and observations pertaining to the toxicity to human beings of DDT and DDT-containing insecticides should be directed to the Industrial Hygiene Research Laboratory.

Questions regarding agricultural uses of the insecticide should be addressed to the chief of the Bureau of Entomology and Plant Quarantine, United States Department of Agriculture, Washington, D. C. Questions involving the contamination of foods with DDT may be sent to the chief of the Division of Pharmacology, Food and Drug Administration, Washington, D. C. The agency legally responsible for enforcement of the Federal Insecticide Act is the Livestock Branch, Production and Marketing Administration, Department of Agriculture, to which questions involving labeling may be directed. Questions regarding insecticidal use of DDT should be referred to the officer in charge, Malaria Control in War Areas, 605 Volunteer Building, Atlanta 3, Georgia.

Two bibliographies listing the literature on DDT are available on request to the Bureau of Entomology and Plant Quarantine, Department of Agriculture. — Reprinted from *Industrial Hygiene News Letter* (September, 1945).

## CORRESPONDENCE

### WAGNER–MURRAY–DINGELL BILL

*To the Editor*: In the July 12 issue of the *Journal* appeared an editorial presenting the results of a questionnaire sent out to all physicians in the Army and Navy at that time. Of those who answered this questionnaire, approximately 20 per cent signified their intention of resuming the general practice of medicine, the balance signifying their intention of taking up the practice of specialized medicine or to continue studies tending in that direction. Of this 20 per cent, it is fair to assume that practically all of them will locate in or near the larger centers of population, where the practice of medicine is less arduous and more profitable and affords freer access to hospitals, clinics, medical schools and other cultural activities.

As a result of this, what is to become of the medical needs of that large proportion of the population who are required to live in the rural and sparsely populated sections of our country? These are the people whose occupations supply largely our raw materials and food and who operate our mines, produce lumber and pulpwood and maintain railroad trackage, roads and other commodities required by our civilization. To them it is not a question of the free choice of a physician, but a question of obtaining one at all in time of emergency. It is this unequal distribution of physicians that Senate Bill 1050, commonly known as the Wagner–Murray-Dingell Bill, is attempting to correct.

This bill has been persistently opposed by the Medical profession in general, the American Medical Association in particular and the medical and surgical supply manufacturers who are reported to be furnishing the funds to promote the defeat of this proposed legislation. Not one constructive adequate substitute for this bill has been presented by the opponents of this measure, nor have they offered constructive helpful criticism tending toward a better solution of the subject.

The Massachusetts Medical Society recently sent to its members a reprint of an article from the *Journal of the American Medical Association* purporting to be an analysis of such portions of this bill as concern the medical profession. This analysis would have been of value had it not interjected its opposing opinions and had it not implied that those physicians who favor this bill are largely of communist leanings. Furthermore, it was stated that the opinion of the officials of the association had not been requested by the sponsors of this bill. Would one consult a dog kennel for an unbiased opinion on the ethics of dogs chasing cats?

Are not the physicians of this country intelligent enough to analyze for themselves a fair and unprejudiced presentation of this bill without having it doctored and tailored to suit the fancy of those bitterly and uncompromisingly opposed to it?

A few years ago the writer, having access to several copies each week of the *Journal of the American Medical Association* wrote to the publishers suggesting that, as a matter of economy and paper saving, his subscription be discontinued. He was promptly informed in a letter that to discontinue his subscription would necessitate the exclusion of his name as a fellow of the American Medical Association. His reply was to the effect that if fellowship in the American Medical Association was a subscription premium from the publishers, he would prefer that his name be omitted. It was!

Organized medicine has gone a long way in raising the standard of health and medical ethics in this country. It has yet a long way to go.

J. Walter Schirmer, M.D.

Needham, Massachusetts

### THE DISCOVERY OF INSULIN

*To the Editor*: On Monday, October 1, Dr. Charles H. Best, of Toronto, addressed nearly five hundred medical students from Boston University, Harvard and Tufts. Dr. Best was introduced by Dr. Joslin, and with his permission, parts of his introductory remarks are appended as being of unusual historical interest.

Reginald Fitz

* * *

*Ladies and Gentlemen*: It is too early to assign the place that the discovery of insulin will take among the great achievements of medicine, but already its importance to the protection of the human race is assured. For diabetes is a universal disease, the full extent of which is only becoming apparent as the average age of the population approaches the decade of life in which the onset of diabetes is most frequent.

The abolition of deaths by infection means that millions of persons who would previously have died are now reaching the period at which the chance of becoming diabetic is greatest. Therefore, a discovery that gives protection from uncontrolled diabetes is analogous to a discovery that would give protection from arteriosclerosis or cancer.

The first patient in New England to receive insulin is here today. At one time she was my severest case. When I first saw her, my average patient of her age lived only six years; she acquired diabetes twenty-eight years ago. As you can see, she continues well and active.

Imagine yourselves as medical students twenty-two years ago, meeting in an amphitheater just as crowded as this to hear another medical student — your guest of today — tell his story. As he revealed what he and Banting had tried to do, their hopes, their fears and their final success, the air was tense with excitement. President Eliot, of Harvard University, was in the front row of listeners. In the midst of the hour I was called out to receive a telegram, which I handed him. At the conclusion of Mr. Best's address, President Eliot, in his never-to-be-forgotten impressive manner, read aloud the telegram. Perhaps you, too, would like to hear it today.

Toronto, Ont. Oct. 26, 1923

Dr. Elliott P. Joslin, 81 Bay State Road, Boston.
At any meeting or dinner please read following. I ascribe to Best equal share in discovery. Hurt that he is not so acknowledged by Nobel trustees. Will share with him.

Banting

Ladies and gentlemen, I have the honor of presenting my friend Dr. Best, who, while a medical student, with Banting discovered insulin and thereby *ipso facto* changed his status from student to investigator.

## NOTICES

### ANNOUNCEMENTS

Dr. Joseph J. Bradley is resuming the practice of gynecology and obstetrics at 39 Bay State Road, Boston 15.

Dr. Knowles B. Lawrence announces the opening of an office on October 15 at 1180 Beacon Street, Brookline.

Dr. Sidney Levin announces the opening of an office at 475 Commonwealth Avenue, Boston.

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Dr. William Curry Moloney announces the opening of an office at 39 Bay State Road, Boston.

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## SUFFOLK DISTRICT MEDICAL SOCIETY

The fall dinner of the Suffolk District Medical Society will be held at the Harvard Club of Boston on Saturday, November 17. Guests will assemble at 6:00 p.m., and dinner will be served promptly at 7:00 p.m. The speaker will be Brigadier General Elliott C. Cutler, M.C., A.U.S., whose subject will be "Experiences in the European Theater of Operations."

This is to be a "home-coming meeting," and all members of the district society are urged to bring as their guests men who have been recently discharged from service or those who are still in uniform; the latter will be admitted without charge, regardless of whether or not they are members of the Massachusetts Medical Society. In addition, the members of other district societies are urged to attend. Tickets may be purchased from the treasurer, Dr. Richard S. Eustis, 319 Longwood Avenue, Boston 15. Contrary to the custom adopted for the past several years, wives of members will not be admitted.

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## MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The fall meeting and dinner of the Massachusetts Society of Examining Physicians will be held on Wednesday, November 7, at 7 p.m. in the State Suite of the Copley Plaza Hotel, Boston. Dr. Eugene E. O'Neil will present a paper, "Painful Extremities: The cause and treatment." Drs. Burton E. Hamilton, William E. Browne, Alexander P. Aitken and Henry C. Marble will discuss the paper.

Reservations for the dinner ($3.50 per person) may be made by writing to Miss Anne Rodman, Assistant Secretary, 157 Fourth Street, Medford, Massachusetts.

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## NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, November 1, at 7:15 p.m. in the classroom of the Nurses' Residence. Dr. Eugene E. O'Neil will speak on the subject "The Diagnosis and Treatment of Venous Thrombosis." Dr. Mary D. Matarazzo will be chairman.

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## LEGISLATIVE CONFERENCE

A meeting to discuss bills relating to health matters will be held on Thursday, December 13, at 10 a.m., at the Gardner Auditorium, State House, under the joint auspices of the Massachusetts Department of Public Health and the Massachusetts Central Health Council. If necessary, the meeting will reconvene at 2 p.m. Physicians, nurses and social workers interested in health promotion are invited to attend.

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## SALMON LECTURES

The current set of Thomas William Salmon Lectures will be given by Dr. Roy Graham Hoskins on three successive Fridays, November 2, 9 and 16, at 8:30 p.m. at the New York Academy of Medicine. The subjects of the three lectures are as follows: "Biology of Man in Relation to Schizophrenia"; "The Pattern of Schizophrenia"; and "The Biological Appraisal of Schizophrenia."

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## AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 2, 1946, at 2:00 p.m. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the secretary by November 1, 1945.

All candidates are now required to be out of medical school eight years, and in that time they must have completed an approved one-year internship and at least three years of approved special formal training, or its equivalent by the preceptorship method under a recognized obstetrician-gynecologist or a diplomate of this board, in the seven years following the intern year. This board's requirements for internships and special training are similar to those of the American Medical Association, since both these organizations are at present co-operating in a survey of acceptable institutions.

A number of changes in regulations and requirements were put into effect at the Board's last annual meeting, held in June, 1945. These were designed to aid civilian candidates as well as those in the armed forces; they have been incorporated in the *Bulletin* of the Board, a copy of which may be obtained from the Secretary's Office, 1015 Highland Building, Pittsburgh 6.

All candidates are required to take the Part I examination, which consists of a written examination and the submission of twenty-five case-history abstracts, and the Part II examination, which consists of an oral, clinical and pathological examination. The Part I examination will be arranged so that the candidate may take it at or near his place of residence, whereas the Part II examination will be held late in May, 1946, or early June, 1946, in that city nearest to the largest group of candidates. The time and place of the latter will be subsequently announced.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6.

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## SOCIETY MEETINGS AND CONFERENCES

### Calendar of Boston District for the Week Beginning Thursday, November 1

Friday, November 2
*9:00–10.00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.
10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Dowling Building. Boston City Hospital.

Saturday, November 3
*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, November 5
*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, November 6
*9:00–10:00 a.m. Medical clinic. Infants' Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

Wednesday, November 7
*12:00 m. Clinicopathological conference. Children's Hospital.
*12:00 m.–1:00 p.m. Clinicopathological conference. Cambridge Hospital.

*Open to the medical profession.

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October 1–December 10, 1945 and January 7–April 22, 1946. Metropolitan State Hospital. Eleventh postgraduate seminar in neurology and psychiatry. Page 314, issue of September 6.

November 1. New England Hospital for Women and Children. Notice elsewhere on this page.

November 2, 9 and 16. Salmon Lectures. Notice elsewhere on this page.

November 7. Massachusetts Society of Examining Physicians. Notice elsewhere on this page.

November 8. Pitfalls and Pleasures in the Treatment of Diabetes. Dr. Elliott P. Joslin. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

November 17. Suffolk District Medical Society. Notice elsewhere on this page.

December 13. Legislative Conference. Notice elsewhere on this page.

February 2. American Board of Obstetrics and Gynecology. Notice elsewhere on this page.

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### District Medical Societies

SUFFOLK
November 17. Harvard Club of Boston.

WORCESTER
November 14. Grafton State Hospital.
December 12. Worcester City Hospital.
January 9. St. Vincent Hospital.
February 13. Worcester State Hospital.
March 13. Worcester Memorial Hospital.
April 10. Hahnemann Hospital.
May 8. Annual meeting.